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UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF WISCONSIN

PROMEGA CORPORATION,

Plaintiff,

and

MAX-PLANCK-GESELLSCHAFT zur FORDERUNG der WISSENSCHAFTEN E.V.,

Involuntary Plaintiff,

v.

LIFE TECHNOLOGIES CORPORATION, INVITROGEN IP HOLDINGS, INC., and APPLIED BIOSYSTEMS, LLC,

Defendants.

Case No. 10-cv-281-bbc

MEMORANDUM IN SUPPORT OF DEFENDANTS' MOTION FOR PARTIAL SUMMARY JUDGMENT OF NONINFRINGEMENT OF THE PROMEGA PATENTS AND ALTERNATIVELY INVALIDITY

CONFIDENTIAL

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I. INTRODUCTION

In the present action, Promega Corporation ("Promega") has alleged that Defendants' AmpFlSTR® kits infringe claims of several of its patents.[1] Defendants now move for partial summary judgment of noninfringement, and alternatively invalidity, on four of the five patents-in-suit—the four so-called Promega patents.

The position Promega has taken regarding the scope of the claims of the Promega patents leads to only two possible outcomes on summary judgment: either the claims are narrow in scope and as a result not infringed, or they are broad in scope and as a result invalid on grounds of non-enablement or obviousness.

The Promega patents generally involve the simultaneous co-amplification, or multiplex amplification, of regions in human DNA known as short tandem repeat (STR) loci. The claims recite methods and materials for multiplexing specific groups or sets of STR loci listed in the claims. However, in the present litigation Promega has taken the position that the Promega patents encompass multiplexing STR loci not even recited in the claims. As Defendants' AmpFlSTR® kits amplify unrecited loci, Promega's overbroad proposed construction is required for it to survive summary judgment of noninfringement. Under a proper, closed construction of the claim term "a set of . . . loci," the claims of the Promega patents do not cover the accused AmpFlSTR® kits because the kits amplify loci not listed in the claims. Summary judgment of noninfringement would therefore be appropriate.

Alternatively, if the claim term "a set of . . . loci" is construed to be open-ended, the Promega patents would be invalid for non-enablement or obviousness. The undisputed facts demonstrate that the prior art disclosed a rudimentary process of trial and error experimentation

[1] The patents-in-suit are U.S. Patent Nos. 5,843,660 ("the '660 patent"); 6,221,598 ("the '598 patent"); 6,479,235 ("the '235 patent"); and 7,008,771 ("the '771 patent") (collectively, "the Promega patents"); and RE37984.

that was unpredictable, laborious, and time consuming. The Promega patents reflect the same process that was taught in the prior art without any additional gains in efficiency or predictability. In short, the Promega patents fail to teach and enable skilled artisans to multiplex arbitrary sets of loci for the simple reason that Promega did not invent such a general method. Summary judgment of invalidity for lack of enablement would therefore be appropriate. On the other hand, if the disclosure of the Promega patents were deemed enabling, the Promega patents would still be invalid on grounds of obviousness because the entirety of their disclosure is found in the prior art.

The material facts are not subject to genuine dispute. Under these facts, Promega cannot have both broad and valid claims or narrow and infringed claims. Therefore, summary judgment that the claims are either not infringed or are invalid is appropriate.

II. STATEMENT OF THE FACTS

A. BACKGROUND ON THE TECHNOLOGY

DNA is a double-stranded molecule consisting essentially of two complementary strands of nucleotides. Proposed Findings of Fact in Support of Defendants' Motion for Summary Judgment of Invalidity and Alternatively Noninfringement ("PFF") ¶ 2. The four nucleotides which are found in DNA are adenine (A), thymine (T), guanine (G), and cytosine (C). PFF ¶ 3. An STR locus is a region of DNA which contains repeats of a particular nucleotide sequence. PFF ¶ 4. For example, the sequence ATT (adenine-thymine-thymine) may be repeated a number of times in tandem (*i.e.*, in a row) at a particular STR locus. Id.

The number of repeats of a given sequence at a particular STR locus varies highly from individual to individual. PFF ¶ 5. Such length and/or sequence variation is referred to as "polymorphism." PFF ¶ 6. A region, or locus, of DNA in which such variation occurs is referred to as a "polymorphic locus." PFF ¶ 7. For example, one individual's DNA may have

eleven CCCG (cytosine-cytosine-cytosine-guanine) repeats at a given STR locus, while another individual may have fourteen at the same locus. Id. Each of these variations is referred to as an "allele" (or "marker") of the particular locus. PFF ¶ 8. Further, each individual has two alleles for every STR locus, one inherited maternally and the other paternally. PFF ¶ 9.

Determining the unique set of alleles at multiple loci in an individual's DNA gives rise to an STR profile or fingerprint unique to the individual. PFF ¶ 10. This method is known as STR profiling and can serve as the basis for identifying individuals, determining whether two samples are a match or originate from two individuals, determining whether one sample contains a mixture of two individuals' DNA, etc. PFF ¶ 11. Consequently, STR profiling is useful in many fields, including forensic science, paternity testing, bone marrow transplant monitoring, cell line authentication, linkage mapping, etc. PFF ¶ 12.

When performing STR analysis, it is necessary to amplify (make copies of) the STR loci of interest in order to obtain a detectable amount for analysis. PFF ¶ 13. For reasons of efficiency, it is advantageous to co-amplify, or multiplex, several loci in a single reaction rather than individually. PFF ¶ 14. Amplification of STR loci is most commonly carried out by the polymerase chain reaction (PCR). PFF ¶ 15. The basic idea of PCR is to (1) separate double-stranded DNA into single strands, (2) allow primers which specifically target the desired STR loci to bind to the single strands at the target loci, (3) replicate the single strands beginning at these primer sites into double-stranded DNA again, and (4) repeat the process until a sufficient amount of copies of the desired STR loci is generated. PFF ¶ 16. In multiplex PCR amplification reactions, multiple STR loci are simultaneously targeted and multiple corresponding primers are used simultaneously in a single reaction. PFF ¶ 17.

B. THE STATE OF THE ART LEADING UP TO THE PROMEGA PATENTS

The concept of multiplex amplification reactions was known prior to the Promega patents. PFF¶ 20. In fact, it far precedes the Promega patents, first emerging in the late 1980s. PFF ¶ 21. The Promega patents explicitly acknowledge this early work and the fact that, by the time of the Promega patents, multiplex reactions had already been "described ***extensively*** in the literature" and "***extensively*** developed" in areas such as deletion screening for certain genetic diseases. Declaration of Amy Sun in Support of Defendants' Motion for Summary Judgment of Invalidity and Alternatively Noninfringement ("Sun Decl."), Ex. 2 ('660 patent), col. 2, ll. 17-21 (emphasis added); Ex. 3 ('598 patent), col. 1, ll. 60-64 (emphasis added).

The concept of multiplexing STR loci also was already known in the art. PFF ¶ 22. The scientific literature abounds with publications describing multiplex reactions of various sets of STR loci. Id. For example, multiplexes of large numbers of loci (*e.g.*, a "highly discriminating octoplex" and even multiplexes of 11 STR loci) had already been described in the prior art. Sun Decl., Ex. 2 ('660 patent), col. 3, l. 10; *see also* Sun Decl., Ex. 4 ('235 patent), col. 3, ll. 7-8; Sun Decl., Ex. 5 ('771 patent), col. 3, ll. 12-13. Again, the Promega patents themselves acknowledge that multiplex amplification of STR loci predate them. Sun Decl., Ex. 2 ('660 patent), col. 3, ll. 46-47 ("[T]here are multiplex amplification procedures for specific loci . . . ."); Ex. 3 ('598 patent), col. 2, ll. 36-37 (same).

However, despite the fact that multiplex PCR was known since the late 1980s and multiplex PCR of STR loci had already been "described extensively in the literature" in the early 1990s, the technology remained a highly unpredictable and experimental one. PFF ¶ 24; Sun Decl., Ex. 2 ('660 patent), col. 2, ll. 17-18; Ex. 3 ('598 patent), col. 1, ll. 60-61. Scientists discovered, rather unexpectedly, that multiplexing a plurality of STR loci was more complicated than simply combining several monoplex reactions into one. PFF ¶ 25. Indeed, multiplexing

introduced new problems and issues which otherwise did not occur when performing reactions in monoplex format. PFF ¶ 26.

Therefore, each new multiplex set had to be tested and optimized through trial and error experimentation. PFF ¶ 30. In fact, until actually attempted, it was neither known nor possible to predict whether the loci in the set were even compatible and would co-amplify together. PFF ¶ 29. It was necessary to develop primer pairs that would co-amplify together and not interfere with each other; eliminate undesirable results such as nonspecific amplification or primer-dimer formation; and adjust a number of reaction parameters such as temperature, the number of amplification cycles, and the concentration of primers, enzyme, buffer, and dNTP. PFF ¶ 33. Primers were the crucial component of any multiplex reaction, and if successful co-amplification could not be achieved by adjusting these parameters, new primer candidates would have to be designed and tested. PFF ¶¶ 34, 35. Identifying primer pairs for each locus that worked together in a multiplex and produced clean results would often take several tries—sometimes many tries—and significant time. PFF ¶ 36.

The same trial and error process was necessary even when adding a single new locus to an already successful multiplex, as again, it could not be predicted how the loci would interact with each other or how effectively and efficiently the primers would work in a multiplex reaction. PFF ¶ 31. Further, creating a successful multiplex became more complicated with the addition of each new locus, *i.e.*, adding an eighth locus to a 7-plex was more complicated than adding a seventh locus to a 6-plex. PFF ¶ 32. As one prior art reference notes, "as more primer sets are added, the permissive reaction conditions have been observed to become increasingly less flexible." Sun Decl., Ex. 16 (Chamberlain '90) at 280. As discussed in greater detail below, the increasing difficulty of expanding a preexisting multiplex is highly pertinent given Promega's

position that the claims of the Promega patents cover unlimited extensions of the sets of loci listed in the claims.

Thus, although scientists had discovered ways of multiplexing specific sets of loci, they had yet to discover a universal method or formula which eliminated the laborious trial and error experimentation required to eliminate or minimize locus to locus imbalance, artifact bands, and other problems. PFF ¶¶ 27, 28. While general guidelines existed, there was no standard protocol which enabled certain, consistent, and clean co-amplification of any arbitrary set of loci. PFF ¶¶ 27, 28, 37.

C. THE PROMEGA PATENTS

The Promega patents purport to be the first to teach the multiplex amplification of certain specific sets of STR loci. PPF ¶ 18. Acknowledging that "there are [already] multiplex amplification procedures for ***specific*** loci" but a "great[] desire[] for the detection of alleles in other types of loci such as [other] ***specific*** STR loci," the Promega patents summarize the claimed inventions as follows:

> It is, therefore, an object of the present invention to provide a method and materials for the simultaneous amplification of multiple ***distinct*** [*i.e.*, specific] polymorphic short tandem repeat (STR) loci . . . . Multiplex analysis of the sets of ***specific*** STR loci disclosed herein have [sic] not been previously described in the prior art.

Sun Decl., Ex. 2 ('660 patent), col. 3, ll. 46-61 (emphasis added); Ex. 3 ('598 patent), col. 2, ll. 36-49 (emphasis added). The "distinct" and "specific STR loci" which Promega characterizes as its invention are those described in the examples in the specifications and listed in the claims.

The '660 patent was filed on June 7, 1999 and is a continuation-in-part of Application No. 08/316,544 ("the '544 parent application"), filed on September 30, 1994 and later abandoned. Sun Decl., Ex. 2 ('660 patent). The '598 patent was filed on April 15, 1996 and is a continuation

of the '544 parent application. Sun Decl., Ex. 3 ('598 patent). The '235 patent was filed on November 25, 1998 and is a continuation-in-part of the application that issued into the '660 patent. Sun Decl., Ex. 4 ('235 patent). The '771 patent was filed on September 6, 2002 and is a division of the application which issued into the '235 patent. Sun Decl., Ex. 5 ('771 patent). Thus, the priority date for the '660 patent is June 7, 1999, the priority date for the '598 patent is September 30, 1994, the priority date for the '235 patent is November 25, 1998, and the priority date for the '771 patent is September 6, 2002.

D. DEFENDANTS' AMPFLSTR® KITS

Promega has accused Defendants of infringing claims of the Promega patents by making, using, selling, and offering to sell the AmpFlSTR® line of kits. *See generally* Dkt. #143 (Second Amended Complaint). This action, filed in response to arbitration proceedings initiated by Defendants, represents the second time Promega has sued Defendants on the '660 and '598 patents, and on many of the same accused products.[2] The accused AmpFlSTR® kits provide components for carrying out the simultaneous amplification (copying) of multiple STR loci from one or more DNA samples. PPF ¶ 1.

The Identifiler® kit amplifies a total of sixteen STR loci: CSF1PO, D5S818, D7S820, D13S317, TPOX, D3S1358, D8S1179, D16S539, D18S51, D21S11, FGA, TH01,[3] vWA,[4] D2S1338, D19S433, and Amelogenin. Sun Decl., Ex. 1.

The Profiler® kit amplifies a total of ten STR loci: D5S818, D7S820, D13S317, D3S1358, D8S1179, D18S51, D21S11, FGA, vWA, and Amelogenin. Id.

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[2] The first litigation was pending before this Court and captioned *Promega Corp. v. Applera Corp*. (01-C-244-C) (W.D. Wis.). Applera Corporation was the predecessor to current Defendant Applied Biosystems, LLC.

[3] The locus TH01 is also denoted HUMTH01.

[4] The locus vWA is also denoted HUMvWA31A and HUMvWFA31.

The Cofiler® kit amplifies a total of seven STR loci: CSF1PO, D7S820, TPOX, D3S1358, D16S539, TH01, and Amelogenin. Id.

Many of the loci amplified by the Identifiler®, Profiler®, and Cofiler® kits are not listed in the claims of the Promega patents. Id.; *see also* Appendix B to this Brief.

III. APPLICABLE LEGAL STANDARDS

A. SUMMARY JUDGMENT

Rule 56 of the Federal Rules of Civil Procedure provides that summary judgment shall be granted if there is "no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." FED. R. CIV. P. 56(a). "By its very terms, this standard provides that the mere existence of some alleged factual dispute between the parties will not defeat an otherwise properly supported motion for summary judgment; the requirement is that there be no genuine issue of material fact." Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 247-48 (1986). Facts which are material are those which "might affect the outcome of the suit under the governing law." Id. at 248. In determining whether any genuine issues of material fact exist, the Court must review the record and construe all facts in the light most favorable to the nonmoving party and draw all reasonable inferences in that party's favor. Heft v. Moore, 351 F.3d 278, 282 (7th Cir. 2003). However, the evidence must create more than "some metaphysical doubt as to the material facts" in order to preclude summary judgment. Springer v. Durflinger, 518 F.3d 479, 484 (7th Cir. 2008).

B. CLAIM CONSTRUCTION

Claim construction is a legal determination to be made by the Court. Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996); Markman v. Westview Instruments, Inc., 52 F.3d 967, 979 (Fed. Cir. 1995) (*en banc*), *aff'd*, 517 U.S. 370 (1996). In construing the

claims, the Court looks first to the intrinsic evidence: the claims, specification, and prosecution history. Teleflex, Inc. v. Ficosa N. Am. Corp., 299 F.3d 1313, 1324-25 (Fed. Cir. 2002).

Claims are generally given their "ordinary and customary" meaning "in the context of the particular claim" and "the context of the entire patent" as a whole, as understood by a person of ordinary skill in the art when the patent application was filed. Phillips v. AWH Corp., 415 F.3d 1303, 1312-13 (Fed. Cir. 2005); ACTV, Inc. v. Walt Disney Co., 346 F.3d 1082, 1088 (Fed. Cir. 2003). The specification "is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." Phillips, 415 at 1315 (quoting Vitronics, 90 F.3d at 1582). The prosecution history also "may affect the scope of the invention." Vitronics, 90 F.3d at 1582. It "can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it otherwise would be." Phillips, 415 F.3d at 1318 (citing Vitronics, 90 F.3d at 1582-83).

Where, as here, multiple patents "derive from the same initial application, the prosecution history regarding a claim limitation in any patent that has issued applies with equal force to subsequently issued patents that contain the same claim limitation." Elkay Mfg. Co. v. Ebco Mfg. Co., 192 F.3d 973, 980 (Fed. Cir. 1999); *see also* Advanced Cardiovascular Sys. v. Medtronic, 265 F.3d 1294, 1305 (Fed. Cir. 2001) ("The prosecution history of a related patent can be relevant if, for example, it addresses a limitation in common with the patent in suit.").

C. PATENT INFRINGEMENT AND VALIDITY

Summary judgment on the issue of infringement "is proper when no genuine issue of material fact exists, in particular, when no reasonable jury could find that every limitation recited in the properly construed claim either is or is not found in the accused device." Irdeto Access, Inc. v. Echostar Satellite Corp., 383 F.3d 1295, 1299 (Fed. Cir. 2004) (citation and internal

quotations omitted). Infringement must be proven by a preponderance of the evidence. Tech. Licensing Corp. v. Videotek, Inc., 545 F.3d 1316, 1327 (Fed. Cir. 2008).

A patent is invalid for lack of enablement when it fails to "enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use" the claimed invention "***as broadly as it is claimed***" and "without undue experimentation." 35 U.S.C. § 112, ¶ 1; In re Vaeck, 947 F.2d 488, 495-96 (Fed. Cir. 1991) (quoting In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988)) (emphasis added); Sitrick v. Dreamworks, LLC, 516 F.3d 993, 999 (Fed. Cir. 2008). A patent is invalid as obvious if the differences between the subject matter of the claimed invention and the prior art are "such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103. Invalidity must be proven by the standard of clear and convincing evidence. Videotek, 545 F.3d at 1327.

IV. ARGUMENT

A. THE CLAIMS SHOULD BE LIMITED TO AMPLIFICATION OF THE SPECIFIC SETS OF LOCI THEY RECITE

In its order construing the claims dated May 24, 2011 (Dkt. #190), the Court deferred construing the claim term "a set of . . . loci" until the summary judgment stage. Sun Decl., Ex. 6 at 5. Defendants now address this outstanding claim construction issue. Defendants' proposed construction for the term "a set of . . . loci" is set forth below:

Claim Term	Proposed Construction
"a set of . . . loci"	a collection of only the loci listed in the claim

In other words, Defendants propose a construction wherein the sets of loci listed in the claims are closed. Moreover, such a closed construction should apply universally to all of the claims of the

Promega patents. As the Court recognized, textual variation between the claims does occur. Sun Decl., Ex. 6 at 5. Nevertheless, a universally closed construction for "a set of . . . loci" is proper because in no case did Promega actually invent multiplex amplification of arbitrary, *i.e.*, open-ended, sets of loci. Promega itself characterizes its alleged inventions as the specific sets of loci listed in the claims. Consequently, an open-ended construction would grant Promega exclusive rights in excess of what Promega actually invented. These and other reasons supporting a universally closed construction for "a set of . . . loci" are discussed fully below.

1. Promega Disavowed Multiplex Reactions of Open-Ended Sets of Loci

The claim term "a set of . . . loci" should be construed as closed because Promega disavowed loci not explicitly recited in the claims. During prosecution, a patentee may have "disclaimed or disavowed subject matter, narrowing the scope of the claim terms." Seachange, Int'l, Inc. v. C-Cor Inc., 413 F.3d 1361 (Fed. Cir. 2005) (citation omitted). For example, disavowal can occur "[w]here an applicant argues that a claim possesses a feature that the prior art does not possess in order to overcome a prior art rejection." Id. at 1372-73 (citation omitted).

In Seachange, the district court's construction of a claim term "network for data communications" was challenged on appeal. The district court had found that the claim language did not explicitly limit the term to "direct, point-to-point interconnections" and further, that the prosecution history did not reflect clear disavowal of non-point-to-point interconnections. Id. at 1368. The Federal Circuit disagreed and reversed.

It noted that during prosecution, the applicant argued that claim 1 ("representative" of a group of claims under rejection)

> recites a method in which at least three processor systems are interconnected using a point-to-point two-way channel interconnection with each of the other processor systems. . . . Neither the point to point two-way channel interconnection nor the arrangement of stored data and redundant data is suggested by the

> combination of Morita and Brenner. . . . Morita . . . does not describe a point to point interconnection. . . . Brenner does not describe that each of the processor systems are interconnected in a point to point two-way channel interconnection . . . .

Id. at 1370-71. The applicant made the same argument with respect to another prior art reference: "[N]owhere in [Gardner] does the patentee describe or suggest a store/retrieve two-way point-to-point configuration" or "interconnecting each of the processors in a point to point configuration." Id. at 1372.

The Federal Circuit held that these facts were sufficient to support a finding of disavowal, *i.e.*, that the patentee had narrowed the scope of the claims to include only point-to-point networks. Id. Despite the fact that the claim language did not expressly exclude non-point-to-point networks, the patentee argued that the claimed invention featured point-to-point networks and that the prior art lacked the same feature. Id. at 1372-73 (holding that disavowal occurs "[w]here an applicant argues that a claim possesses a feature that the prior art does not possess in order to overcome a prior art rejection") (citation omitted). Essentially, "by distinguishing the claimed invention over the prior art, an applicant is indicating what the claims do not cover, [and] he is by implication surrendering such protection." Id. at 1373 (citation and internal quotations omitted). Thus, the patentee in Seachange, by distinguishing the claimed invention from the prior art on the basis of point-to-point connections, implicitly surrendered, *i.e.*, disavowed, non-point-to-point networks from the scope of the claims.

Promega made many such similar statements of disavowal during prosecution of the Promega patents. For example:

- "Caskey *et al.* do not teach these combinations of loci as claimed. Consequently, Caskey *et al.* do not anticipate claims 1 or 19 as amended." Sun Decl., Ex. 11 at 271 (emphasis added).
- "Applicants admit that several of the loci sets listed [in Oetting et al.] include one or two of the individual loci listed in the group of loci from which the set of loci is

> selected for co-amplification and evaluation according to the method of claim 1. . . . However, Applicants submit that it takes more than the disclosure of some of the individual loci in the various sets of loci co-amplified according to the present claims for any given reference to anticipate the claims." Sun Decl., Ex. 12 at 234-35 (emphasis added).

- "Appellants note that while some of the individual loci described in these three multiplexes also appear in the appealed claims, it has been admitted that the Kimpton *et al.* reference does not teach the specific locus ***combinations*** claimed." Sun Decl., Ex. 11 at 328 (emphasis added).

- "Oldroyd et al. in fact discloses experimental results obtained from co-amplifying and evaluating seven STR loci simultaneously, a set of loci which includes the loci HUMVFA31/A and HUMTH01, but which does not include any other loci included in the list of loci provided in claim 1 as originally filed." Sun Decl., Ex. 12 at 234.

Many other similar statements pervade the prosecution histories of the Promega patents. A comprehensive collection is provided as Appendix A to this brief.

In these statements, Promega is describing a feature of the claimed invention—the specific sets of loci listed in the claim—which Promega argues the prior art lacks. Promega argued over and over that its own specific sets of loci were distinct from the specific sets of loci found in the prior art. *See* Appendix A. It did not matter if a prior art reference used some loci which overlapped with the loci claimed in the Promega patents. According to Promega, only a prior art reference which taught the exact same sets of loci as those in the claims, without other loci, would anticipate the claims. Id. As explained in Seachange, "by distinguishing the claimed invention over the prior art, an applicant is indicating what the claims do not cover, [and] he is by implication surrendering such protection." Seachange, 413 F.3d at 1373 (citation and internal quotations omitted). Promega, by distinguishing its claimed inventions on the basis of the specific sets or combinations of loci listed in each of the claims, therefore indicated that the claims only cover the specific sets of loci recited and not sets of loci having overlapping but also unlisted loci. It thus surrendered all such unlisted loci from the scope of the claims. Id. The sheer volume of statements of disavowal by Promega, summarized in Appendix A, cannot be

lightly brushed aside. An open-ended claim construction in the face of such overwhelming evidence would constitute clear error.

2. The Examiner Characterized the Alleged Inventions as the Specific Sets of Loci Listed in the Claims

An examiner's statement of reasons for allowance is important to claim construction because it constitutes a part of the prosecution history and, as such, reflects the ongoing dialogue between the applicant and the United States Patent and Trademark Office on the merits of the application and claimed invention. In Elkay, another case where a disavowal was found on appeal, Elkay the patentee argued that a claim limitation regarding "an upstanding feed tube" was not limited to a single tube. Elkay, 192 F.3d at 978-79. The district court had agreed with Elkay, however, the Federal Circuit reversed and vacated the district court's claim construction based on a finding of disavowal during prosecution. Id. Elkay had distinguished its claimed invention from the prior art based on the argument that the prior art taught separate feed tubes for liquid and air. Id. Therefore, the Federal Circuit concluded that "Elkay gave up a construction of the feed tube/probe limitation that could include an apparatus with separate flow paths for liquid and air." Id. at 978.

More to the point, it considered Elkay's argument that its own statements made during prosecution were "insignificant" to be "particularly unpersuasive" given the examiner's statement of reasons for allowance. Id. at 979. Specifically, the examiner stated that

> the prior art of record does not teach a container support with a . . . feed tube as claimed wherein the feed tube has a passage means which both dispenses liquid . . . and admits air . . . . [The prior art] does not provide a means for admitting air. Note that [the prior art] provides a separate conduit for exterior air . . . .

Id. Thus, the examiner allowed the claims "because he understood"—based on Elkay's arguments—"the claim to describe a single feed tube with a single flow path for both liquid and air." Id. Elkay never responded to the examiner's statement. Id.

During prosecution of the '598 patent, it was also the examiner's understanding that the alleged inventiveness of the claimed inventions derived from the specific sets of loci listed in the claims. When the examiner issued a notice of allowance for the '598 patent, she explained in her statement of reasons for allowance:

> [T]he art does not teach the ***specific combinations provided in the claims***. Furthermore, as found in the declaration submitted by Cynthia Sprecher, unexpected results were obtained. While ***all*** of the ***instant STR loci were known*** in the art at the time the invention was made, the ***combinations of STR loci of the instant claims*** for use in multiplex amplification and [sic] was ***not contemplated***. . . . Therefore . . . the instant claims are allowable.

Sun Decl., Ex. 13 at 239 (emphasis added). Thus, the examiner recognized that "all" of the STR loci claimed by Promega already "were known," but instead understood the novelty and nonobviousness of the claimed inventions to lie in the "specific combinations [of loci] provided in the claims." Id. As was the case in Elkay, Promega never responded to this statement or indicated in any other manner that the statement was incorrect. Therefore its present arguments that the claims should be construed to include unlisted loci must be considered "particularly unpersuasive." Elkay, 192 F.3d at 979. The proper construction for the term "a set of . . . loci" is "a collection of only the loci listed in the claim."

3. The Actual (Alleged) Inventions Are Only the Specific Sets of Loci Listed in the Claims

It must be remembered that claims should be construed so that they "secure to the patentee his ***actual invention***." Smith v. Snow, 294 U.S. 1, 14 (1935) (emphasis added). *See also* Phillips v. AWH Corp., 415 F.3d 1303, 1321 (Fed. Cir. 2005) ("The patent system is based

on the proposition that the claims cover ***only the invented subject matter***.") (emphasis added); Acumed, LLC v. Stryker Corp., 483 F.3d 800, 815 (Fed. Cir. 2007) (advising that "[p]atent scope should be coextensive with what the inventor invented"). In other words, claims must not be construed so as to unduly narrow the scope of the claims or, as is the danger here, to grant the patentee exclusive rights beyond what was actually invented. Retractable Techs., Inc. v. Becton, No. 2010-1402, 2011 U.S. App. LEXIS 13925 at *21 (Fed. Cir. July 8, 2011) ("[W]e strive to capture the scope of the actual invention, rather than strictly limit the scope of claims to disclosed embodiments or allow the claim language to become divorced from what the specification conveys is the invention.") (citing Phillips, 415 F.3d at 1323-24).

In the prior Promega-Applera litigation, Promega itself admitted that it "did not 'invent'" or even claim multiplex reactions using loci not listed in the claims. Sun Decl., Ex. 21 at 15 ("Promega's claimed inventions are the successful multiplex reactions that employ the various ***sets of loci as identified in the claims***.") (emphasis added); id. at 9 ("[I]t is clear that Promega ***did not 'invent'*** co-amplification of all of the sets of loci present in Defendants' accused products at the time of the invention of the Promega patents . . . .") (emphasis added).

Moreover, during prosecution (as opposed to its present litigation-driven theory) Promega characterized its alleged inventions as the specific sets of loci found in the examples and listed in the claims. In the applications that eventually led to the Promega patents, Promega acknowledges that multiplexing had already been "described ***extensively*** in the literature," even at the time the earliest two of the Promega patents were filed. Sun Decl., Ex. 2 ('660 patent), col. 2, ll. 17-18 (emphasis added); Sun Decl., Ex. 3 ('598 patent), col. 1, ll. 60-61 (emphasis added). In fact, many—and in the case of the '598 patent, "all"—of the specific loci claimed in the

Promega patents were already known and had been multiplexed in the prior art. PFF ¶¶ 39, 40.[5] Additionally, several of the primers used to multiplex the loci claimed in the Promega patents were also already known in the art.[6] PFF ¶ 93.

Therefore, the claimed novelty of the Promega patents lay in the narrow discovery of methods and materials for multiplexing the specific sets of loci listed in the claims. In its own words, Promega summarized its inventions as follows:

> It is, therefore, an object of the present invention to provide a method and materials for the simultaneous amplification of multiple ***distinct*** polymorphic short tandem repeat (STR) loci using PCR or other amplification systems to determine, in one reaction, the alleles of each locus contained within the multiplex. Multiplex analysis of the ***sets of specific STR loci disclosed herein*** have not been previously described in the prior art.

Sun Decl., Ex. 2 ('660 patent), col. 3, ll. 54-61 (emphasis added); *see also* Sun Decl., Ex. 3 ('598 patent), col. 2, ll. 43-49; Sun Decl., Ex. 4 ('235 patent), col. 4, ll. 22-32; Sun Decl., Ex. 5 ('771 patent), col. 4, ll. 27-37.

In other words, Promega did not represent that alleged inventions provide broadly applicable or universal methods and materials for co-amplifying any arbitrary choice of loci but rather only "distinct" and "specific STR loci." Moreover, by emphasizing that the specific sets of loci disclosed allegedly "[had] not been previously described in the prior art," Promega made clear that these sets of loci are the "actual invention[s]" of the Promega patents to the extent Promega actually invented anything. Smith, 294 U.S. at 14. It would be unfair now construe

[5] As just one example, one of the prior art references raised during prosecution of the Promega patents disclosed a multiplex of four STR loci known as HUMFESFPS, HUMTH01, HUMF13A01, and HUMVWFA31. Sun Decl., Ex. 12 at 242. All of these loci are recited in various claims of the Promega patents. *See generally* Sun Decl., Ex. 2 ('660 patent), cols. 63-70; Sun Decl., Ex. 3 ('598 patent), cols. 35-42; Sun Decl., Ex. 4 ('235 patent), cols. 57-62; Sun Decl., Ex. 5 ('771 patent), cols. 59-62.

[6] Again, as just one example, another prior art reference raised during prosecution of the Promega patents disclosed "primers identical to the primers of SEQ ID NO: 1, 2, 9, 15, 16, 19, 20, 27, 28, and 30." Sun Decl., Ex. 13 at 105.

these sets of loci as open-ended in contradiction to Promega's public representations. The claim element "a set of . . . loci" should be construed to include only the loci listed in the claims.

4. The Transition Phrase "Comprising" Does Not Render Every Single Claim Element Open-Ended

The above discussion supports a universally closed construction for the individual claim term "a set of . . . loci," regardless of the textual variation in the claims. This is not negated by the fact that some claims utilize the transition phrase "comprising." While the term "comprising" may signify that the recited elements of a claim are "nonexclusive," it "does not reach into [and] render every word and phrase" within the individual claim elements open-ended. Dippin' Dots, Inc. v. Mosey, 476 F.3d 1337, 1343 (Fed. Cir. 2007). *See also* Sandisk Corp. v. Kingston Tech. Co., Inc., No. 10-cv-243-bbc, 2011 U.S. Dist. LEXIS 27696, at *59 (W.D. Wis. Mar. 15, 2011) ("The rule does not mean steps already present described in the claim can be broadened; it means only that an accused product may perform additional steps *not* claimed."). In other words, it is the claim which is (presumptively) open-ended with respect to claim elements, not the claim elements themselves which are open-ended. Infringement of a "comprising" claim is not avoided if a device includes elements beyond the recited claim elements. Dippin' Dots, 476 F.3d at 1343. Infringement is avoided, however, if each individual claim element "as recited" is not satisfied. Id.

A "comprising" claim was asserted by the patentee in Dippin' Dots. The claim involved a "method of preparing and storing a free-flowing, frozen alimentary dairy product, comprising the steps of: (1) preparing an alimentary composition for freezing; (2) dripping said alimentary composition into a freezing chamber; (3) freezing said alimentary composition into beads; (4) storing said beads at a temperature at least as low as -20 degrees F. so as to maintain said beads free-flowing for an extended period of time; (5) bringing said beads to a temperature between

substantially -10 degrees F. and -20 degrees F. prior to serving; and (6) serving said beads for consumption at a temperature between substantially -10 degrees F. and -20 degrees F. so that said beads are free flowing when served." Dippin' Dots, 476 F.3d at 1340.

The district court had construed the term "beads" to mean "small frozen droplets . . . which have a smooth, spherical (round or ball shaped) appearance." Id. At 1342-43. "[I]rregular or odd shaped particles such as 'popcorn'" were excluded from the construction of "beads." Id. at 1343. The district court granted summary judgment of noninfringement because the accused processes produced both spherical and irregular shaped particles. Id.

On appeal, the patentee argued that the district court erred in its claim construction. Id. Based on the presence of the term "comprising" in the preamble of the claim, according to the patentee, the term "beads" should not have been limited to processes which produce only spherically shaped particles. Id. The Federal Circuit affirmed the district court's claim construction, reasoning:

> "Comprising" is not a weasel word with which to abrogate claim limitations. "Comprising" appears at the beginning of the claim – "comprising the steps of" – and indicates here that an infringing process could practice other steps in addition to the ones mentioned. Those six enumerated steps must, however, all be practiced ***as recited*** in the claim for a process to infringe. The presumption raised by the term "comprising" [*i.e.*, that the list of elements is nonexclusive] ***does not reach into each of the six steps to render every word and phrase therein open-ended*** . . . .

Id. (emphasis added) (citations and internal quotations omitted).

In Dippin' Dots, therefore, while the term "comprising" meant that the method steps of the claim were nonexclusive, it did not render the individual claim elements open-ended. A process could infringe the claim by performing additional steps beyond "freezing," "storing," and "serving" the "beads," but not by producing, freezing, storing, or serving anything other than

"beads." The accused process, which failed to satisfy the individual "beads" claim element "as recited," was held not to infringe.

The same principles are directly applicable to the claims presently at issue. The method claims of the Promega patents recite various steps for "selecting," "co-amplifying," and "evaluating" "a set of . . . loci." *See generally* Sun Decl., Ex. 2 ('660 patent), cols. 63-70; Sun Decl., Ex. 3 ('598 patent), cols. 35-42; Sun Decl., Ex. 4 ('235 patent), cols. 57-62; Sun Decl., Ex. 5 ('771 patent), cols. 59-62. The kit claims recite "primers" for co-amplifying "a set of . . . loci." Id. The term "comprising" is used throughout. Id.

What follows from Dippin' Dots is clear. The steps of the method and the contents of the kit are nonexclusive (presumptively). An infringing kit, for example, may contain additional components such as enzymes, buffers, and allelic ladders. *See*, *e.g.*, Sun Decl., Ex. 2 ('660 patent), col. 16, ll. 29-42; Sun Decl., Ex. 3 ('598 patent), col. 10, l. 61 – col. 11, l. 8; Sun Decl., Ex. 4 ('235 patent), col. 16, ll. 39-52; Sun Decl., Ex. 5 ('771 patent), col. 16, l. 57 – col. 17, l. 3. Likewise an infringing process may perform additional steps not claimed. However, the word "comprising" does not reach into individual claim elements, including the "a set of . . . loci" claim element, and render them open-ended. Dippin' Dots, 476 F.3d at 1343. Consequently, broadly construing the term "a set of . . . loci" as an open set is not justified. Id. The proposed construction "a collection of only the loci listed in the claim" respects the contours of the claims by ensuring that "comprising" is not operative upon the individual claim elements as recited. It is therefore the proper construction.

5. The First Claim Construction Order from the Prior Litigation Is Correct

In the earlier Promega-Applera litigation, the Court correctly construed certain method steps of the claims of the '660 and '598 patents as closed with respect to unrecited loci. Sun Decl., Ex. 7. However, on motion for reconsideration by Promega, the Court issued a second

claim construction order holding instead that the method steps were open-ended. Sun Decl., Ex. 22. In the present litigation, the Court ruled that the earlier claim constructions are not binding, however, the Court also suggested that Defendants "explain why they believe [the second claim construction] is flawed if they wish to persuade the same court to reach a different conclusion this time around." Sun Decl., Ex. 6 at 4-5.[7]

Since the previous litigation, subsequent Federal Circuit case law such as Dippin' Dots has clarified that the transition phrase "comprising" does not render every element within a claim open-ended. This could not be more true than in the present case. The flaw in the second claim construction is that, by construing individual claim elements as open-ended, it created a direct conflict with the explicit claim language. The second claim construction order specifies: "Claims 1 through 5 and 16 of the '660 Patent require the presence of at least one of the sets identified in the *Markush* groups stated in limitation (b) of those claims but do not exclude the presence of other STR loci in the multiplex reaction required by limitation (c) of those claims." Sun Decl., Ex. 22 at 10. Steps (b) and (c) of claim 16 of the '660 patent, for example, recite:

> (b) selecting a set of three short tandem repeat loci of the DNA sample to be analyzed which can be amplified together, wherein the set of three loci is selected from the group of sets of loci consisting of:
>
> D3S1539, D19S253, D13S317;
> D10S1239, D9S930, D20S481;
> D10S1239, D4S2368, D20S481;
> D10S1239, D9S930, D4S2368;
> D16S539, D7S820, D13S317; and
> D10S1239, D9S930, D13S317. [sic]
>
> (c) co-amplifying the three loci in the set in a multiplex amplification reaction, wherein ***the*** product of the reaction ***is*** a mixture of amplified alleles from each of the co-amplified loci ***in the set***;

[7] Defendants in fact addressed the error in the second claim construction in their response claim construction brief. *See* Dkt. #187 at 6-8.

Sun Decl., Ex. 2 ('660 patent), col. 66, ll. 23-37 (emphasis added). Under the second claim construction, the "co-amplifying" step could include additional loci not selected in the "selecting" step. In other words, step (c) was not limited solely to the loci chosen in step (b); step (c) itself was instead construed to be open-ended.

However, the claim language explicitly limits the loci co-amplified in step (c) to only the loci selected in step (b). Step (c) states: "***the product*** of the reaction ***is*** a mixture of amplified alleles from each of the co-amplified loci in ***the set***." Sun Decl., Ex. 2 ('660 patent), col. 66, ll. 35-37 (emphasis added). The phrase "***the*** product of the reaction" means that there is one and only one reaction product. Further, the claim defines not what the single product "comprises" or "includes" but rather what it "***is***," which means that what follows is comprehensive as well as exclusive. What "***the*** product of the reaction ***is***" is "a mixture of amplified alleles from each of the co-amplified loci in ***the set***." The language "in the set" finds antecedent basis in the "set" recited in step (b). Therefore, the set of loci co-amplified in step (c) must be the same as the set of loci selected in step (b). Because the loci in step (b) are limited to the sets of loci listed in the claim (by virtue of the Markush group structure), the loci of the "co-amplifying" step are likewise limited.[8]

[8] The claims of the '598 patent originally recited "the product of the reaction," like the '660 and other Promega patents. However, during prosecution the examiner found this instance of the word "the" to be indefinite for lack of antecedent basis. Sun Decl., Ex. 13 at 101. Promega amended the claims to recite "thereby producing" to overcome the rejection. Id. at 153. In reality the rejection was uncalled for, as the word "the" was not an invalid reference to a nonexistent antecedent (indeed, it would not make sense for there to by *any* product of the reaction preceding the co-amplifying step). Rather, the word "the" signifies that there is only a single, exclusive reaction product generated from the co-amplification step. As Promega intended "thereby producing" to be an equivalent of and substitution for "the product of the reaction," the above argument with respect to "the product of the reaction" applies equally to the '598 patent.

Moreover, step (b) requires that the loci selected in that step "can be amplified together," highlighting the interconnectedness of the selection step and co-amplification step. It simply would not make sense to select one set of loci and then amplify a different set. The reason particular loci "which can be amplified together" are selected in step (b) is so that those particular loci are amplified together in step (c).

The language in the claims makes it clear that the set of loci in step (b) is the exact same set of loci in step (c), without addition, subtraction, or variation. The first claim construction from the earlier litigation was consistent with the claims in this respect. The second claim construction, which permitted divergence between the loci in step (b) and step (c), conflicts with the language of the claims and therefore should not be adopted in the present case.

6. A Universally Open-Ended Construction for "A Set of . . . Loci" Is Not Appropriate

A universally closed-ended construction of "a set of . . . loci" is proper for the reasons discussed above. However, to the extent the Court construes the term as open-ended, such a construction should not apply universally to all of the claims.

All of the asserted claims of the '660 patent and some of the asserted claims of the other Promega patents are written in Markush format or depend from claims written in Markush format.[9] The bedrock principle that "[a] Markush group by its nature is closed" should not be one alterable by claim construction because it is a fundamental law of claim drafting. Gillette Co. v. Energizer Holdings, Inc., 405 F.3d 1367, 1372 (Fed. Cir. 2005). It would not be an understatement to say that construing a claim written in Markush format as open-ended would abolish certainty in claim interpretation and defeat the public notice function of patents.

[9] These claims are claims 1, 2, 3, 4, 5, 9, 16, 17, 19, 20, 21, 23, 24, 25, 27, 28, 29, 30, and 31 of the '660 patent and claims 1, 2, 4, 5, 6, 7, 8, 9, and 10 of the '598 patent.

Other claims, such as claim 3 of the '660 patent, recite specific limitations such as "wherein the set of at least four loci co-amplified therein ***is a set of six loci***," or claim 16 of the '660 patent, which requires selecting exactly and not at least "a set of three" loci.[10] Sun Decl., Ex. 2 ('660 patent, col. 64, ll. 34-35; col. 66, l. 23) (emphasis added). To construe "a set of . . . loci" in claim 3 as open-ended and permit a set of seven, eight, nine, or more loci to fall within the meaning of the claim would be to completely write out the limitation "is a set of six loci." Courts, however, "do not rewrite claims; instead, [they] give effect to the terms chosen by the patentee." Helmsderfer v. Bobrick Washroom Equip., Inc., 527 F.3d 1356, 1364 (Fed. Cir. 1999) (citation omitted). As such, an open-ended construction of the term "a set of . . . loci" must not apply to claim 3 of the '660 patent, other similarly worded claims, and claims which depend from these claims.

In sum, while a universally closed construction for "a set of . . . loci" is proper for the reasons discussed above, a universally open-ended construction is not. If an open-ended claim construction is to be adopted, certain textual differences in the claims should not be disregarded. Where the claims would otherwise be closed based on Markush format or other specific language, claim construction should not be seized upon as an opportunity to override and rewrite such language. Effect must be given to the terms chosen by the patentee, and accordingly for these claims, the claim term "a set of . . . loci" must be construed as closed. Helmsderfer, 527 F.3d at 1364.

[10] These claims and the claims which depend from these claims are claims 2, 3, 4, 16, 17, 19, 20, 21, 23, and 24 of the '660 patent.

B. THE ACCUSED PRODUCTS DO NOT INFRINGE THE ASSERTED CLAIMS OF THE PROMEGA PATENTS BECAUSE THEY AMPLIFY LOCI NOT LISTED IN THE ASSERTED CLAIMS

Promega takes the position that the claims of the Promega patents cover multiplex reactions using loci which are not even spelled out in the claims. According to Promega, any number of loci may be added to the sets of loci listed in the claims of the Promega patents and would still be covered by the claims. Further, the choice of which specific loci are added is not critical; so long as the loci listed in the claims are present, any other loci and in any increasing number may be added to the multiplex set and would still fall within the ambit of the claims.

The sole basis of Promega's infringement theory is an open-ended claim construction of the term "a set of . . . loci." In other words, not a single one of the asserted claims would be infringed *but for* an open-ended claim construction. Expanding the reach of the claims to include omitted—indeed, surrendered—subject matter (in full contradiction to its own statements during prosecution) is the *only* way Promega can sustain a basis for infringement against Defendants. *See supra* Part IV.A.1. For the reasons discussed above, such an expansion of claim scope would be improper. As shown below, under a proper, closed-ended construction of "a set of . . . loci," there is no genuine issue of material fact that any of the asserted claims of the Promega patents are infringed by any of the accused products.

1. The Identifiler® Does Not Infringe the Asserted Claims of the '660 Patent Because It Amplifies Loci Not Listed in the Asserted Claims

The asserted claims of the '660 patent are claims 2, 3, 4, 5, 9, 16, 17, 19, 20, 21, 23, 24, 25, 27, 28, 29, 30, and 31. Only the Identifiler® is alleged to infringe claims of the '660 patent. Under a correct construction wherein unrecited loci are excluded from the scope of the claim term "a set of . . . loci," the Identifiler® does not meet the limitations required by all of the asserted claims because it amplifies loci not listed in each of the asserted claims. These loci are

listed in Appendix B of this brief. *See also* Sun Decl., Ex. 1. No genuine issues of material fact exist in this regard. Therefore, summary judgment of noninfringement of the asserted claims of the '660 patent is warranted.

2. The Accused Products Do Not Infringe the Asserted Claims of the '598 Patent Because They Amplify Loci Not Listed in the Asserted Claims

The asserted claims of the '598 patent are claims 1, 2, 4, 5, 6, 7, 8, 9, 10, 12, 15, 19, 21, 22, 23, 24, 27, 28, 31, 32, and 33. The Identifiler®, Profiler®, and Cofiler® products are alleged to infringe the claims of the '598 patent. Under a correct construction wherein unrecited loci are excluded from the scope of the claim term "a set of . . . loci," the Identifiler®, Profiler®, and Cofiler® do not meet the limitations required by all of the asserted claims because they amplify loci not listed in each of the asserted claims. Sun Decl., Ex. 1; Appendix B. No genuine issues of material fact exist in this regard. Therefore, summary judgment of noninfringement of the asserted claims of the '598 patent is warranted.

3. The Identifiler® Does Not Infringe the Asserted Claims of the '235 Patent Because It Amplifies Loci Not Listed in the Asserted Claims

The asserted claims of the '235 patent are claims 1, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, 17, 18, 19, 21, 22, and 23. Only the Identifiler® is alleged to infringe claims of the '235 patent. Under a correct construction wherein unrecited loci are excluded from the scope of the claim term "a set of . . . loci," the Identifiler® does not meet the limitations required by all of the asserted claims because it amplifies loci not listed in each of the asserted claims. Sun Decl., Ex. 1; Appendix B. No genuine issues of material fact exist in this regard. Therefore, summary judgment of noninfringement of the asserted claims of the '235 patent is warranted.

4. The Identifiler® Does Not Infringe Claim 5 of the '771 Patent Because It Amplifies Loci Not Listed in the Asserted Claims

Only claim 5 of the '771 patent is asserted, and only against the Identifiler®. Under a correct construction wherein unrecited loci are excluded from the scope of the claim term "a set of . . . loci," the Identifiler® does not meet the limitation required by claim 5 because it amplifies loci not listed in claim 5. Sun Decl., Ex. 1; Appendix B. No genuine issues of material fact exist in this regard. Therefore, summary judgment of noninfringement of the asserted claims of the '771 patent is warranted.

C. THE PROMEGA PATENTS ARE INVALID UNDER 35 U.S.C. § 112

A general method of multiplexing arbitrary sets of loci was not known in the prior art. PPF ¶¶ 27, 28. Moreover, as discussed below, and as Promega argued in obtaining allowance of asserted claims, multiplexing arbitrary sets of loci based on what actually was known in the prior art would have required undue experimentation (without any guarantee of ultimately succeeding). The Promega patents do not teach anything about multiplexing STR loci beyond what was already known in the prior art. Therefore, to attempt to multiplex arbitrary (*i.e.*, unlisted) loci based on the disclosure of the Promega patents would also have required undue experimentation. Consequently, the Promega patents fail to satisfy the enablement requirement and are invalid.[11] Wands, 858 F.2d at 737.

[11] The scope of the § 112 enablement inquiry is not whether the Promega patents teach and enable multiplex PCR or multiplex PCR of STR loci, as these techniques were already known in the prior art. PFF ¶¶ 20-22. Nor is the issue whether the Promega patents teach and enable the multiplex amplification of the specific sets of loci listed in the claims and taught in the working examples (Defendants do not concede that they do). Instead, the issue is whether the Promega patents teach and enable persons of ordinary skill in the art to multiplex STR loci not listed in the claims, such that their disclosure is at least commensurate with the scope of the claims as asserted by Promega. Vaeck, 947 F.2d at 495-96; Sitrick, 516 F.3d at 999.

1. The Parties Agree on the Level of Ordinary Skill in the Art

The parties agree that a person of ordinary skill in the art pertaining to the Promega patents would have had a bachelor's degree in biology, biochemistry, molecular biology, or related fields, or the equivalent. PFF ¶ 19. Additionally, she would have several years of experience working in a laboratory and be familiar with basic DNA manipulation techniques, primer design, PCR, and multiplex PCR. Id. She would further be familiar with DNA detection techniques such as gel electrophoresis, capillary electrophoresis, fluorescent dye labeling, and genetic testing. Id.

2. Multiplexing Arbitrary Sets of Loci Was Not Known in the Prior Art and Would Have Required Undue Experimentation

As discussed in the Statement of the Facts section, multiplex reactions were carried out through a rudimentary process of trial and error experimentation, where reaction parameters were adjusted on an *ad hoc* basis because there was no way to predict how the loci in a given multiplex would interact with each other. *See* PPF ¶¶ 24-37. A general method for multiplexing arbitrary sets of loci was not known in the prior art. In fact, as Promega admits, attempting to multiplex arbitrary sets of loci would have entailed undue experimentation.

During prosecution, the claims of the Promega patents were subjected to repeated rejection based on examples of successful multiplex reactions already taught in the prior art. Promega's argument to overcome the prior art was therefore that designing and successfully carrying out a multiplex reaction was an unpredictable, labor-intensive process involving extensive trial and error and adjustment of numerous possible reaction parameters. As such, no relationship could be drawn between one successful multiplex reaction, *i.e.*, the prior art, and another, *i.e.*, the multiplex reactions disclosed in the Promega patents.

For example, Promega stated: "[T]he selection of STR loci which could be amplified together was ***not a trivial matter***, but required a ***considerable amount of experimentation***, at the time the present invention was made." Sun Decl., Ex. 13 at 181 (emphasis added). Promega further stated that "screening was required to ensure ***any given set*** of STR loci could be amplified and evaluated together" and that such screening, *i.e.*, experimentation, was "***far from routine***." Sun Decl., Ex. 14 at 247, 249 (emphasis added); Sun Decl., Ex. 13 at 178. (A comprehensive collection of similar statements is found in Appendix C of this brief.) Therefore, undue experimentation would have been required to multiplex arbitrary sets of loci.

As shown below, the Promega patents do not teach beyond what was already known in the prior art, and therefore undue experimentation would also have been required to multiplex arbitrary (unlisted) loci based on the disclosure of the Promega patents. Summary judgment of invalidity for lack of enablement is accordingly warranted. Wands, 858 F.2d at 737.

3. The Promega Patents Do Not Actually Teach and Enable Beyond What Was Already Known in the Prior Art

a. Allele Overlap

The Promega patents state that in designing a multiplex reaction, one should take into account allele overlap. Sun Decl., Ex. 2 ('660 patent), col. 12, ll. 34-36; Ex. 3 ('598 patent), col. 6, ll. 7-9; Ex. 4 ('235 patent), col. 8, ll. 61-64; Ex. 5 ('771 patent), col. 9, ll. 5-8. Allele overlap occurs when alleles of different STR loci are similar in size and thus overlap each other when they are visualized, rendering assignment of alleles to a specific locus difficult or impossible. PFF ¶ 38.

This much, and more, was already well-known in the prior art. For example, one prior art reference, referred to herein as "Edwards," teaches that "fragment sizes should be selected so that they may be separated easily from each other" but not so different in size that they cannot be

visualized on the same gel. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 15; Sun Decl., Ex. 20 (Edwards) at S67. In other words, selection of STR loci should take into account the size range of the alleles, so as to prevent allele overlap between alleles of different loci. Edwards also teaches that in the case of overlapping size ranges, fluorescently labeled primers may be used to distinguish overlapping alleles by color. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 15; Ex. 20 (Edwards) at S67. In addition, another prior art reference, referred to herein as "Kimpton '94," teaches that STR loci having "complex compound repeat regions" and "alleles which differ by only a single base" make it difficult to unambiguously assign alleles. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 15; Ex. 17 (Kimpton '94) at 303. On the other hand, using loci which contain "relatively simple repeat sequences and display regularly spaced alleles" will tend to enable "unambiguous allele designation." Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 15; Ex. 17 (Kimpton '94) at 303.

b. Adequate Product Yield

The Promega patents state that in designing a multiplex reaction, one should take care to ensure adequate product yield. Sun Decl., Ex. 2 ('660 patent), col. 12, l. 43; Ex. 3 ('598 patent), col. 6, l. 15; Ex. 4 ('235 patent), col. 9, l. 14; Ex. 5 ('771 patent), col. 9, l. 3. This merely states the obvious. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 16. Without adequate product yield, an allele which is present obviously could fail to visualize, producing a false negative. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 16.

Moreover, this much, and more, was already well-known in the prior art. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 17. For example, Kimpton '94 teaches that reducing the concentration of template DNA results in reduced product yield, and to varying degrees depending on each locus. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 17; Ex. 17 (Kimpton '94) at 306-07. Kimpton '94 also teaches that product yield is "directly related to the number of PCR

cycles employed," however, some loci will "remain constant" and not amplify beyond a certain number of cycles while others "continue[] to increase with cycle number." Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 17; Ex. 17 (Kimpton '94) at 307. This can result in different levels of amplification products, *i.e.*, locus to locus imbalance. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 17; Ex. 17 (Kimpton '94) at 307. Edwards also teaches that insufficient primer specificity could cause reduced amplification at the target site (primer-template mismatch), resulting in low product yield and low intensity bands. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 17; Ex. 20 (Edwards) at S67.

c. Obtaining True Alleles

The Promega patents state that in designing a multiplex reaction, one should try to avoid generating fragments which do not represent true alleles, *i.e.*, false positives. Sun Decl., Ex. 2 ('660 patent), col. 12, ll. 43-44; Ex. 3 ('598 patent), col. 6, ll. 15-16; Ex. 4 ('235 patent), col. 9, l. 4; Ex. 5 ('771 patent), col. 9, l. 15.

This much, and more, was already well-known in the prior art. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 19. For example, Kimpton '94 demonstrates that skilled artisans were already well aware of spurious artifact bands indistinguishable from expected or true alleles. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 19; Ex. 17 (Kimpton '94) at 309. In addition, Kimpton '94 teaches that "non-specific background amplification," producing spurious bands, may occur as a result of exceeding a particular enzyme concentration. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 19; Ex. 17 (Kimpton '94) at 306. Edwards also teaches that if the primer sequences are not sufficiently specific, nonspecific amplification may occur at non-target sequences of DNA, resulting in spurious bands. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 19; Ex. 20 (Edwards) at S67.

d. Slippage, a.k.a. Stutter

The '660 patent states that the loci selected for use in a multiplex reaction "should produce minimal slippage (*e.g.*, from misreading the repeat sequence during an amplification)." Sun Decl., Ex. 2 ('660 patent), col. 13, ll. 33-35.

This much, and more, was already well-known in the prior art. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 21. For example, one prior art reference, referred to herein as "Kimpton '93," discusses the problem of artifactual stutter banding. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 21; Ex. 18 (Kimpton '93) at 17. Kimpton '93 teaches that stutter banding may be caused by enzyme slippage and that the degree of slippage varies by individual locus. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 21; Ex. 18 (Kimpton '93) at 17. Further, Kimpton '93 teaches that stutter banding occurs with higher frequency when multiplexing dinucleotide repeats, but can be "significantly reduced" by using tri-, tetra-, and pentanucleotide STR loci. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 21; Ex. 18 (Kimpton '93) at 20. Kimpton '94 also teaches that tri-, tetra-, and pentameric STR loci produces cleaner results than dinucleotide STR loci because they are "less prone to artifactual 'stutter' banding." Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 21; Ex. 17 (Kimpton '94) at 303.

e. Base Addition/Deletion

The Promega patents state that loci selected for use in a multiplex reaction should produce "few if any artifacts due to the addition or deletion of a base to the amplified alleles during the multiplex amplification step." Sun Decl., Ex. 2 ('660 patent), col. 13, ll. 35-37; Ex. 4 ('235 patent), col. 10, ll. 6-8; Ex. 5 ('771 patent), col. 10, ll. 15-17.

This much, and more, was already well-known in the prior art. Sun Decl., Ex. 8 (Struhl Invalidity Report), ¶ 23. For example, Kimpton '93 discusses the problem of double bands and teaches that the cause is extra base addition during amplification. Sun Decl., Ex. 8 (Struhl

Invalidity Report) ¶ 23; Ex. 18 (Kimpton '93) at 17-18. Further, Kimpton '93 teaches various strategies to eliminate double bands, including cleavage of the amplification product and adjustment of various reaction parameters. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 23; Ex 18 (Kimpton '93) at 18-19. None of these strategies is taught in the Promega patents. In addition, Kimpton '94 teaches that "non-template dependent addition" of an extra base to the amplified loci appears to "decrease with increased dNTP concentration." Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 23; Ex. 17 (Kimpton '94) at 306. Kimpton '94 suggests that this is "probably directly related to the amount of free Mg^{2+} ions present, with the enzyme [Taq polymerase] being apparently less efficient at non-template dependent extra base addition at low free Mg^{2+} concentrations." Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 23; Ex. 17 (Kimpton '94) at 306. Kimpton '94 even suggests an optimal dNTP concentration of 800 μ*M*. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 23; Ex. 17 (Kimpton '94) at 306.

f. Primer Synthesis

With regard to primer synthesis, the '660 and '598 patents acknowledge that "[s]ynthesis of primers used in the present method can be conducted using any standard procedure for oligonucleotide synthesis known to those skilled in the art." Sun Decl., Ex. 2 ('660 patent), col. 13, ll. 6-8; Ex. 3 ('598 patent), col. 7, ll. 11-12. Therefore, the Promega patents state explicitly that they do not teach anything beyond the prior art about how to synthesize primers.

This much, and more, was already well-known in the prior art. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 24. Primer synthesis began with the target sequence to which the primer was being designed to hybridize, and properties such as sequence, length, and annealing temperature could be modified using computer software available at the time, for example, Oligo™. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 24; Ex. 15 (Chamberlain '88) at 14; Ex. 26 (Gill *e al*.) at 1547. Kimpton '94 and Kimpton '93 teach that primers could also be

synthesized commercially. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 24; Ex. 17 (Kimpton '94) at 303; Ex. 18 (Kimpton '93) at 13; Ex. 19 (Caskey), col. 5, ll. 22-24. Another reference, referred to herein as "Caskey," teaches that primers "can occur naturally" or be "produced synthetically." Id. In addition, Caskey teaches that the "[s]ensitivity and specificity of the oligonucleotide primers are determined by primer length and uniqueness of sequence within a given sample of template DNA." Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 24; Ex. 19 (Caskey), col. 5, ll. 34-37. Caskey recommends primers that are "usually about greater than 15 mer [*i.e.*, 15 bases in length] and in the preferred embodiment are about 20 to 30 mer in length." Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 24; Ex. 19 (Caskey), col. 5, ll. 39-40. Finally, Caskey teaches that "[a]lthough primer sequence need not reflect the exact sequence of the template [*i.e.*, target sequence], the more closely the 3' end reflects the exact sequence, the better the binding during the annealing stage." Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 24; Ex. 19 (Caskey), col. 5, ll. 50-53.

g. Problems Related to Primers

With regard to problems arising from inappropriate primers, the Promega patents state:

> Inappropriate selection of primers can produce several undesirable effects such as lack of amplification, amplification at multiple sites, primer dimer formation, undesirable interaction of primer sequences from different loci, production of alleles from one locus which overlap with alleles from another, or the need for amplification conditions or protocols for the different loci which are incompatible in a multiplex.

Sun Decl., Ex. 2 ('660 patent), col. 12, l. 66 – col. 13, l. 6; Ex. 3 ('598 patent), col. 7, ll. 4-11; Ex. 4 ('235 patent), col. 11, ll. 25-32; Ex. 5 ('771 patent), col. 11, ll. 35-42.

This much, and more, was already well-known in the prior art. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 26. For example, Kimpton '94 teaches primer concentrations for a given locus were "directly related" to band intensities for the alleles of the locus and, moreover, could

effect an increase or decrease in amplification of the other loci in the multiplex as well. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 26; Ex. 17 (Kimpton '94) at 305. Kimpton '94 also notes that "[a]t the higher primer concentration artifact primer-dimer bands were observed with increased frequency." Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 26; Ex. 17 (Kimpton '94) at 305; 308-09. Primer-dimer formation was also linked to temperature at specific points during the amplification reaction. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 26; Ex. 17 (Kimpton '94) at 305; 308-09. In addition, Edwards teaches that primer sequence is crucial to the success of a multiplex reaction. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶¶ 10, 26; Ex. 20 (Edwards) at S67. If the primer sequence is not sufficiently specific, nonspecific amplification may occur at non-target sequences of DNA, producing spurious bands, while reduced amplification may occur at the target site (primer-template mismatch), resulting in low intensity bands for authentic alleles. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶¶ 10, 26; Ex. 20 (Edwards) at S67. Edwards further teaches that nonspecific primer binding can be minimized by adding Tween 20 and Triton X-100, ß-mercaptoethanol, and tetramethylammonium chloride to the reaction. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶¶ 10, 26; Ex. 20 (Edwards) at S68. Regarding primer-dimer formation, Edwards teaches that "[m]ultiple sets of primers increase the possibility of primer complementarity at the 3' ends, leading to 'primer-dimers.' These artifacts deplete the reaction of dNTPs and primers and outcompete the multiplex amplicons for polymerase. This effect can be reduced by titrating primer concentrations and cycling conditions." Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 26; Ex. 20 (Edwards) at S69.

h. The Reiterative Process of Selecting and Developing Primers

The '235 and '771 patents state: "Primers are preferably developed and selected for use in the multiplex systems of the invention by employing a re-iterative process of selecting primer sequences, mixing the primers for co-amplification of the selected loci, co-amplifying the loci,

then separating and detecting the amplified products." Sun Decl., Ex. 4 ('235 patent), col. 11, ll. 36-41; Ex. 5 ('771 patent), col. 11, ll. 46-51. The '235 and '771 patents further state that these "re-iterative selection processes" are simply "repeated until a complete set of primers is identified" which cleanly and evenly co-amplify all the loci in the set. Sun Decl., Ex. 4 ('235 patent), col. 12, ll. 25-28; Ex. 5 ('771 patent), col. 12, ll. 36-38. These disclosures are not found in the '660 and '598 patents.

This much, and more, was already well-known in the prior art. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 28. Kimpton '93 teaches that successful amplification of all the loci in each multiplex was achieved through the same re-iterative optimization process, including adjustment of primer concentration and annealing temperature. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 28; Ex.18 (Kimpton '93) at 19. Edwards teaches that "[c]onditions for each set of primers should be developed individually and modified if necessary as primer sets are added." Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 28; Ex. 20 (Edwards) at S68. Further, "if equimolar primer concentrations do not yield uniform amplification signals for all fragments, the concentration of some primer pairs can be reduced in relation to others." Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 28; Ex. 20 (Edwards) at S68. In fact, primer concentration "will almost certainly have to be refined empirically." Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 28; Ex. 20 (Edwards) at S68. Caskey also teaches that conditions must be "optimized for each reaction." Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 28; Ex. 19 (Caskey), col. 6, l. 65.

i. Achieving Locus to Locus Balance

The '235 and '771 patents state that employing the re-iterative process outlined above may result in problems such as imbalanced amplification of alleles, *i.e.*, locus to locus imbalance. Sun Decl., Ex. 4 ('235 patent), col. 11, ll. 42-43; Ex. 5 ('771 patent), col. 11, ll. 52-53. The '235 and '771 patents state:

> Locus to locus balance is also affected by a number of parameters of the amplification protocol such as the amount of template used, the number of cycles of amplification, the annealing temperature of the thermal cycling protocol, and the inclusion or exclusion of an extra extension step at the end of the cycling process. Absolutely even balance across all alleles and loci is generally not achieved.

Sun Decl., Ex. 4 ('235 patent), col. 12, ll. 9-15; Ex. 5 ('771 patent), col. 12, ll. 19-25.

This much, and more, was already well-known in the prior art. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 30. For example, Kimpton '94 teaches that "approximately even signal intensities" can be achieved by "adjustment of individual primer concentrations." Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 30; Ex. 17 (Kimpton '94) at 303, 309. Kimpton '93 also found that "[c]omparable signal intensities" could be obtained by "adjustment of individual primer concentrations." Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 30; Ex. 18 (Kimpton '93) at 16-17. Kimpton '93 further teaches that variation in the signal intensities for allele bands of an individual locus may occur, with the larger allele usually exhibiting a less intense signal. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 30; Ex. 18 (Kimpton '93) at 17. The cause was suggested to be the "preferential amplification of smaller sequences during PCR." Id. Finally, Edwards teaches that locus to locus imbalance may be exacerbated over numerous amplification cycles, with shorter sequences typically amplifying better than longer sequences. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 30; Ex. 20 (Edwards) at S68-S69. Edwards then teaches that "[t]his effect can be circumvented by initiating PCR with the long amplicon primers and by adding the primer for the shorter some cycles later, or by using a low concentration of the short amplicon primer." Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 30; Ex. 20 (Edwards) at S69.

j. Primer Concentration

Regarding primer concentration, the '235 and '771 patents state:

> Generally, increasing primer concentration for any particular locus increases the amount of product generated for that locus.

> However, this is also a reiterative process because increasing yield for one locus may decrease it for one or more other loci. Furthermore, primers may interact directly affecting yield of the other loci. Linear increases in primer concentration do not necessarily produce linear increases in product yield for the corresponding locus.

Sun Decl., Ex. 4 ('235 patent), col. 12, ll. 1-8; Ex. 5 ('771 patent), col. 12, ll. 11-18.

This much, and more, was already well-known in the prior art. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 32. For example, Kimpton '94 teaches primer concentrations for a given locus were "directly related" to band intensities, *i.e.*, the amount of product generated, but also that adjusting the concentration of one primer could also effect an increase or decrease to varying, *i.e.*, nonlinear, degrees in amplification of other loci in the multiplex. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 32; Ex. 17 (Kimpton '94) at 305.

k. Multiplexing Unlisted Loci

It is undisputed that adding new loci to a multiplex becomes increasingly complicated with each new locus. PPF ¶ 32. Thus, Promega admits that the Promega patents do not teach a method for co-amplifying open-ended sets of loci which would accommodate unlisted loci, and instead merely direct skilled artisans to a process of "trial and error" which was already well-known: "[s]uccessful combinations [of loci] in addition to those disclosed herein can be generated by ***trial and error*** of locus combinations, by selection of primer pair sequences, and by adjustment of primer concentrations to identify an equilibrium in which all included loci may be amplified." Sun Decl., Ex. 2 ('660 patent), col. 12, ll. 46-50 (emphasis added); Ex. 3 ('598 patent), col. 6, ll. 17-20 (emphasis added); Ex. 4 ('235 patent), col. 9, ll. 6-10 (emphasis added); Ex. 5 ('771 patent), col. 9, ll. 17-21 (emphasis added). A disclosure which provides nothing more than a direction to engage in trial and error experimentation using techniques already well-

known in the art cannot meet the enablement standard as a matter of law. Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1374 (Fed. Cir. 1999).

General guidelines for multiplexing STR loci which could be applied to any set of loci already existed in the prior art. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 34. First, Edwards points out that while designing some new multiplex reactions "may be as simple as combining two sets of primers for which reaction conditions have been determined separately," others are not so simple and "must be developed with careful consideration for the regions to be amplified, the relative sizes of the fragments, the dynamics of the primers, and the optimization of PCR technique to accommodate multiple fragments." Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 34; Ex. 20 (Edwards) at S66. Next, Edwards teaches a "step-by-step" method for developing a multiplex reaction:

1. **Choose Loci**. Determine PCR system. Distribute amplicons (localized at mutation hot spots, linked to genes, chromosomally unlinked, grouped close exons in a single amplicon, etc.). Design internal control fragment(s) (other exons, external sequences, host sequence, sequence conserved in all target templates, etc.).

2. **Position Primers** in regions of detailed sequence; in relation to amplicon sizes.

3. **Design Primers** with similar reaction kinetics.

4. **Develop PCR Conditions Separately** for each primer set.

5. **Add Primer Sets Sequentially**, altering conditions as necessary. Reduce nonspecific amplification (hot start, ionic detergents, short extension times, hottest annealing, reselect primer sequence). Vary relative concentrations of primer sets for equal amplification. Change buffer systems if necessary.

6. **Adjust** reaction components and cycling conditions for multiplex amplification. Mg^{2+}, dNTP, and polymerase requirements may increase. Ideal extension times may be longer.

Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 34; Ex. 20 (Edwards) at S67.

Edwards provides further detail in connection with each step. For example, regarding primers, Edwards teaches that they should be designed to have similar reaction kinetics, *i.e.*, so that they will all function under uniform conditions during a single multiplex reaction and amplify their respective target sequences. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 35; Ex. 20 (Edwards) at S67-S68. Edwards suggests a G/C (guanine/cytosine) content between 40-60% and a primer length of 23-28 nucleotides, but teaches that primer concentrations and temperatures "will almost certainly have to be refined empirically." Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 35; Ex. 20 (Edwards) at S68. Edwards notes that "the possibility of nonspecific priming and other artifacts is increased with each additional primer" such that "primer pairs that give a 'clean' signal alone [may] produce artifact bands in multiplex." Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 36; Ex. 20 (Edwards) at S68. Caskey also teaches that primers should be "composed of similar GC base compositions and lengths." Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 35; Ex. 19 (Caskey), col. 6, ll. 59-60.

l. Evidence from the Earlier Litigation

As mentioned previously, the instant action represents the second time in which Promega has sued Defendants on the '660 and '598 patents. In the prior litigation, Professor Richard Gibbs offered his expert opinion regarding the invalidity of the '660 and '598 patents. Co-inventor Ann Lins was also deposed.

i. Professor Gibbs Found that the Conclusory Disclosure of the Promega Patents Merely Provided Skilled Artisans with an Invitation to Experiment

Like Dr. Struhl, it was Professor Gibbs' opinion that "the field of multiplex PCR reactions involving STR loci was highly unpredictable in that one of skill in the art would not know, absent a specific pre-existing teaching, whether a given multiplex would successfully co-amplify until the co-amplification reaction was attempted and successfully performed." Sun Decl., Ex.

25 (Gibbs Report) at 17; *see also* id. at 23. Therefore, "great reliance" was placed on "empirical experimentation," *i.e.*, trial and error. Id. at 17, 23. Professor Gibbs also agreed that to achieve a successful multiplex reaction could require "many repetitions of experiments, each with slightly different conditions." Id. at 18, 23. He further agreed that "the process of creating a multiplex becomes more complicated with the addition of each new STR loci [sic] to the multiplex." Id. Again, this point is particularly material given Promega's assertion that the claims of the Promega patents cover unlimited extensions of the sets of loci listed in the claims.

In view of this technological landscape, Professor Gibbs found "the only statements in the specification concerning how to build a larger multiplex from an established multiplex" to be "conclusory." Id. at 27. For example, Professor Gibbs noted the following statements from the specification of the '598 patent:

> Once a multiplex containing two loci is developed, it may be used as a core to create multiplexes containing more than two loci. . . . Many other derivative multiplexes can be generated based upon a working multiplex. The derivative multiplexes, are, in some sense, routine extensions of the core multiplex.

Id. at 27 (quoting '598 patent, col. 7, l. 15 – col. 8, l. 7). In Professor Gibbs' opinion, this "conclusory statement" fails to provide "any information concerning how to choose appropriate loci for the larger multiplex." Id. Ultimately, he concluded that the '598 patent

> merely provides an ***invitation*** for those of skill in the art ***to experiment*** with various undisclosed loci combinations until a combination is chosen which can be successfully co-amplified, and shown to work well in a multiplex amplification reaction. . . . [The '598 patent] ***does not indicate*** to one of skill in the art that the ***inventors had invented the full scope of what [Promega] claim[s]***.

Id. at 27-28 (emphasis added). Professor Gibbs' discussion and opinions with respect to the '660 patent are identical in substance to those regarding the '598 patent. *See* id. at 32-36.

ii. Co-Inventor Ann Lins Admitted that Promega Never Made Any Improvements to the State of the Art

The possibility that the Promega patents actually teach and enable multiplex amplification of unlisted loci is highly doubtful in light of the testimony of co-inventor Ann Lins. During the entire period of time she worked at Promega, 1992-1999, she testified that she "always" utilized the same process of trial and error and that she never developed any ways to increase predictability in the process or shortcuts that made the process any more efficient and streamlined:

> Q: Do you remember any change during your career at Promega as to how much work you had to put in to creating new multiplexes?
>
> A: It was always trial and error.
>
> . . .
>
> Q: Did you ever develop any shortcuts to determining which loci would work in a multiplex from when you originally made the CTT [multiplex] to when you added [loci] to it?
>
> . . .
>
> A: Shortcut methods, no.
>
> Q: Did your ability to predict which multiplexes that you worked on at Promega would decrease, increase or stay the same over the course of your career at Promega?
>
> . . .
>
> A: Ability to predict would stay the same.
>
> Q: And is that true for the Promega group generally based on your direction with Dr. Schumm and the others?
>
> . . .
>
> A: Based on my experience it stayed the same.

Sun Decl., Ex. 27 (Lins. Depo.) at 8:8-9, 18:20-21, 65:24-67:17.

One cannot discern based on this testimony any advance in the state of the art contributed by Promega in the seven year period between 1992-1999, the general time period during which the Promega patents were allegedly invented. In short, nothing about the process of developing a successful multiplex got any better at Promega during this time frame. Promega managed to multiplex certain specific sets of loci using the known process, but this is beside the point. The point is that the process used by Promega to multiplex those sets of loci was known in the prior art and still in use by its contemporaries, and that Promega did not contribute any advance or improvement to that which was already known.

4. Under Promega's Own Logic, The Promega Patents Fail to Satisfy the Enablement Requirement

As discussed above, according to Promega, despite whatever teaching or guidance can allegedly be found in the Promega patents, "any" new multiplex still would have been "inventive" over such contemporaneous disclosure. *See supra* Part IV.A.iii.b. If any new multiplex set would have been novel and nonobvious and, in Promega's own words, "a patentee ***cannot enable*** inventions that are non-obvious from the patentee's own invention," Sun Decl., Ex. 21 at 13 (emphasis added), then new multiplex sets containing loci not listed in the claims of the Promega patents are not enabled by the Promega patents. Taking Promega's own assertion that the claims of the Promega patents cover new multiplex sets (*i.e.*, unlisted loci), the Promega patents must be deemed invalid for failure to satisfy the enablement requirement of § 112.

Furthermore, according to Promega, in order to be enabling, a disclosure must affirmatively provide the specific reaction conditions for a particular multiplex. During prosecution, Promega argued that a certain reference "[did] not provide an enabling disclosure" because it "fail[ed] to provide any details" about "primers, primer concentration, about preferred reaction conditions to prevent allele overlap, adverse primer-primer interaction, unequal

amplification, accumulation of non-specific PCR products, etc." Sun Decl., Ex. 14 at 248. Therefore, given the unpredictability of the art and the numerous possible reaction parameters, only a reference that provided the specific details for a multiplex reaction would have constituted an enabling disclosure for that reaction. The Promega patents reflect the same general guidelines already known in the prior art but fail to provide detailed reaction conditions for unlisted loci. Therefore, based on Promega's own standard of enablement, the Promega patents are invalid for failure to satisfy the enablement requirement.

D. THE PROMEGA PATENTS ARE INVALID UNDER 35 U.S.C. § 103

In the event that the Promega patents are actually deemed teach and enable skilled artisans to multiplex sets of loci other than those listed in the claims, *i.e.*, arbitrary sets of loci, then the claims would have been obvious in light of the prior art because the prior art would have already taught and enabled the same. Sun Decl., Ex. 8 (Struhl Invalidity Report) ¶ 45. In other words, if trial and error as disclosed in the Promega patents constitutes an enabling disclosure for multiplexing arbitrary sets of loci, then the prior art, which already taught trial and error, would also already have taught multiplexing of arbitrary sets of loci.

1. The Independent Method Claims of the Promega Patents Would Have Been Obvious in View of Caskey and Kimpton '93

The asserted independent method claims of the Promega patents are claims 1 (which is unasserted but from which a number of asserted dependent claims depend) and 16 of the '660 patent, claims 1 and 12 of the '598 patent, and claims 1 and 13 of the '235 patent. *See generally* Sun Decl., Ex. 2 ('660 patent); Ex. 3 ('598 patent); Ex. 4 ('235 patent). These claims all recite four common steps of (1) obtaining a DNA sample, (2) selecting a set of loci to be co-amplified, (3) co-amplifying the set of selected loci, and (4) evaluating the results to determine the alleles present. Id.

a. The Independent Method Claims of the Promega Patents Would Have Been Obvious in View of Caskey

Caskey describes the steps of a multiplex reaction in a way that closely mirrors method steps of the Promega patents: "extracting DNA from a sample to be tested; performing multiplex polymerase chain reaction on the extracted DNA; and identifying the amplified extension products from the multiplex polymerase chain reaction for each different sequence, wherein each different sequence is differentially labelled [sic]." Sun Decl., Ex. 19 (Caskey), col. 3, ll. 23-28.

Delving more specifically into each of the method steps, Caskey describes the step of obtaining a DNA sample: "The source of the genomic DNA to be tested can be any medical or forensic sample." Id. col. 6, ll. 14-16. Caskey goes on to define "forensic sample" and "medical sample" and provide examples of each. Id. col. 6, ll. 16-27.

Caskey describes the step of selecting a set of loci to be co-amplified. For example, Caskey describes that various STR sequences may be "selected" for use in a multiplex reaction according to the claimed invention. Id. col. 3, l. 35.

Caskey describes the step of co-amplifying the set of selected loci by means of "multiplex polymerase chain reaction" (mPCR). Id. col. 6, ll. 34-68.

Finally, Caskey describes the step of evaluating the results to determine the alleles present in the sample. For example, "allele designations were made" for multiplex reactions described in the examples and shown in Figure 3. Id. col. 13, ll. 64-65 and Fig. 3.

Caskey describes each of the steps of the independent method claims of the Promega patents. The only differences are in the number of loci and some the specific loci selected and co-amplified (there are some overlapping alleles, such as HUMFABP and HUMTH01). However, these differences are insignificant. First, the method taught in Caskey is not described in connection with any specific STR loci and therefore is generally applicable to any arbitrary set

of loci. In fact, Caskey states that the method "is applicable to ***any*** sample from which amplifiable DNA can be extracted" and furthermore, that multiplex reactions utilizing certain specific STR sequences are merely "[s]pecific embodiments" of the invention and not the invention itself. Id. col. 3, ll. 29-34 (emphasis added).

Moreover, in both the Promega patents and Caskey, the basic process utilized to multiplex STR loci is the same and the Promega patents do not indicate that there is anything particular or different about multiplexing the sets of loci listed in the claims as opposed to other loci. Id.

In addition, to the extent that the Promega patents do not recite additional loci and yet are deemed enabling with respect thereto, Caskey must also be deemed enabling with respect to multiplexing undisclosed loci, *i.e.*, the loci listed in the claims of the Promega patents.

Finally, the selection of the number of loci and the specific loci for use in a multiplex is merely an arbitrary choice depending on the purpose or design of a given experiment. As the examiner stated during prosecution, "[t]he choice of loci combinations is arbitrary and simply depends upon what information is desired from the allele analysis." Sun Decl., Ex. 11 at 246, 287. A skilled artisan would simply have selected STR loci for a multiplex reaction based on the criteria that were important for the project or task at issue. Therefore, the purely arbitrary differences between the Promega patents and Caskey are such that the independent method claims of the Promega patents would have been obvious and therefore invalid. Id.

b. The Independent Method Claims of the Promega Patents Would Have Been Obvious in View of Kimpton '93

Kimpton '93 describes three successful multiplex reactions employing a total of fourteen different STR loci. Sun Decl., Ex. 18 at 13.

Kimpton '93 describes the step of obtaining a DNA sample: "DNA was prepared from whole blood . . . . Blood samples were obtained from unrelated Caucasians, Afro-Caribbeans, and Asians residing within the United Kingdom." Sun Decl., Ex. 18 (Kimpton '93) at 14.

Kimpton '93 describes the step of selecting a set of loci to be co-amplified: Multiplex 1 is a 4-plex utilizing the following loci: HUMvWA31, HUMTH01, HUMF13A1, and HUMFES/FPS. Id. Multiplex 2 is a 7-plex utilizing the following loci: HUMCD4, HUMDHFR, HUMCYARO3, HUMAPOAII, HUMPLA2A, HUMIIDA, and HUMFABP. Id. Multiplex 3 is a 3-plex utilizing the following loci: HUMGABA, D21S11, and HUMACTBP2. Id. at 15.

Kimpton '93 describes the step of co-amplifying the set of selected loci. Id. at 14 ("PCR amplification was performed . . . ."). Indeed, the title of the article indicates the subject matter "Multiplex Amplification of Short Tandem Repeat Loci." Id. at 13. The specific reaction conditions for each of the three multiplex reactions is described in detail. Id. at 14-15.

Finally, Kimpton '93 describes the step of evaluating the results to determine the alleles present in the sample. For example, for twelve of the loci, "unambiguous allele designation was possible." Id. at 16. Figure 1 contains electrophoretograms displaying the PCR products of the multiplex reactions. Id. at 15.

Therefore, Kimpton '93 describes each of the steps of the independent method claims of the Promega patents. The only differences are in the number of loci and some the specific loci selected and co-amplified (there are some overlapping alleles, such as HUMvWA31 and HUMTH01). However, for the same reasons as discussed above with respect to Caskey, these differences are insignificant. Therefore, the purely arbitrary differences between the Promega patents and the prior art are such that the independent method claims of the Promega patents would have been obvious and therefore invalid. Id.

2. Claims 2, 3, 4, and 5 of the '660 Patent and Claim 4 of the '235 Patent Would Have Been Obvious in View of Caskey and Kimpton '93

Claim 2 of the '660 patent recites the additional limitation "wherein the set of at least four loci-co-amplified is a set of four loci." Sun Decl., Ex. 2 ('660 patent). Claim 3 recites the same limitation except that the set "is a set of six loci." Id. Claim 4 recites the same limitation except that the set "is a set of seven loci." Id. Claim 5 recites the same limitation except the set "is a set of at least eight loci." Id.

As discussed above with respect to the independent method claims of the Promega patents, the number of loci selected to include in a multiplex is arbitrary. *See supra* Part IV.D.1. Further, the method of Caskey does not impose any limits on the number of loci which may be included in a multiplex set and therefore reads on the additional limitations of claims 2, 3, 4, and 5. Id. Therefore, Caskey reads on the additional limitations of claims 2, 3, 4, and 5 which recite specific numbers of loci, and these claims would have been obvious in view of Caskey.

Because the choice of the number of loci is arbitrary, *see supra* Part IV.D.1, Kimpton '93 also reads on the additional limitations claims 2, 3, 4, and 5 which recite specific numbers of loci. Claims 2, 3, 4, and 5 therefore would have been obvious in view of Kimpton '93.

Claim 4 of the '235 patent depends from claim 1 and recites the additional limitation "wherein the set of loci selected in step (b) further comprises a locus which can be used to identify the gender of at least one source of the DNA provided in step (a)." Sun Decl., Ex. 4 ('235 patent). As discussed above with respect to the independent method claims of the Promega patents, the selection of specific loci to include in a multiplex is arbitrary. *See supra* Part IV.D.1. Therefore, Caskey and Kimpton '93 read on the additional limitation of claim 4 which recites a specific type of locus. Claim 4 of the '235 patent would therefore have been obvious in view of Caskey and Kimpton' 93.

3. Claims 9, 17, and 19 of the '660 Patent, Claim 2 of the '598 Patent, and Claims 7, 8, and 15 of the '235 Patent Would Have Been Obvious in View of Caskey and Kimpton '93

Claim 9 of the '660 patent depends from claim 6 (unasserted) which depends from claim 1. Claim 6 recites the additional limitation "wherein the multiplex amplification reaction is done using at least four pair [sic] of primers flanking the at least four loci analyzed." Sun Decl., Ex. 2 ('660 patent). Claim 9 recites the additional limitation "wherein the multiplex amplification reaction is a polymerase chain reaction." Id. Claim 17 depends from independent claim 16 and is similar to claim 6 except that the additional limitation requires exactly "three pair [sic] of primers." Id. Claim 19 also depends from claim 16 and, like claim 9, recites the additional limitation "wherein the multiplex amplification reaction is a polymerase chain reaction." Id.

Amplification of an STR locus requires a corresponding pair of primers. PPF ¶¶ 16, 33-36. Therefore, a multiplex reaction using "three" or "at least four pair [sic] of primers" will correspond to three or at least four STR loci. For the reasons discussed above with respect to the independent method claims of the Promega patents, Caskey encompasses multiplex reactions of three and at least four loci, and thus three and at least four primers, and therefore reads on the additional limitations of claims 6 and 17. *See supra* Part IV.D.1. Moreover, Caskey teaches that amplification may be carried out by means of PCR and therefore reads on the additional limitations of claims 9 and 19. Sun Decl., Ex. 19 (Caskey), col. 6, ll. 34-68. For these reasons, Claims 9, 17, and 19 of the '660 patent would have been obvious in view of Caskey.

Kimpton '93 discloses a 3-plex, a 4-plex, and a 7-plex and therefore necessarily describes "three" and "at least four" primer pairs. Sun Decl., Ex. 18 (Kimpton '93) at 14-15. Kimpton '93 thus reads on the additional limitations of claims 6 and 17 of the '660 patent. Moreover, Kimpton '93 discloses that multiplex amplification was carried out through PCR and thus reads on the additional limitations of claims 9 and 19. Id. The only differences between claims 9, 17,

and 19 and Kimpton '93 are found in the independent claims from which claims 9, 17, and 19 depend. These differences are trivial, as discussed above. *See supra* Part IV.D.1. For these reasons, claims 9, 17, and 19 of the '660 patent would have been obvious in view of Kimpton '93.

Claim 2 of the '598 patent depends from claim 1 and, like claim 19 of the '660 patent, recites the additional limitation "wherein in step (b), the at least three loci are co-amplified by multiplex polymerase chain reaction. Sun Decl., Ex. 3 ('598 patent). For the reasons just discussed, claim 2 of the '598 patent would have been obvious in view of Caskey and Kimpton '93.

Claim 7 of the '235 patent depends from claim 1 and, similar to claims 9 and 17 of the '660 patent, recites the additional limitation "wherein the multiplex amplification reaction is done using pairs of oligonucleotide primers flanking the loci analyzed." Sun Decl., Ex. 4 ('235 patent). Claim 8 of the '235 patent depends from claim 7, which itself depends from claim 1. Similar to claim 19 of the '660 patent, it recites the additional limitation "wherein the set of loci is co-amplified using a polymerase chain reaction." Id. Claim 15 of the '235 patent depends from claim 13 and recites the same additional limitation as claim 8. Id. For the reasons just discussed, claims 7, 8, and 15 of the '235 patent nd would have been obvious in view of Caskey and Kimpton '93.

4. Claim 20 of the '660 Patent, Claim 4 of the '598 Patent, and Claims 12 and 16 of the '235 Patent Would Have Been Obvious in View of Caskey and Kimpton '93

Claim 20 of the '660 patent depends from claim 16 and recites the additional limitation "wherein the amplified alleles are evaluated by comparing the amplified alleles to a size standard, wherein the size standard is selected from the group of size standards consisting of a DNA marker and a locus-specific allelic ladder." Sun Decl., Ex. 2 ('660 patent).

Caskey discloses both an "external standard" as well as an "internal standard . . . composed of labeled alleles of the STR loci of interest," *i.e.*, a locus-specific allelic ladder. Sun Decl., Ex. 19 (Caskey), col. 7, ll. 13-19. Internal standards can be "generated by pooling amplification products from individuals of known genotype such that the molar ratios of each allele observed were approximately equal" (*i.e.*, having even band intensities). Id. col. 19, ll. 15-19. Caskey therefore reads on the additional limitation of claim 20. Caskey also reads on independent method claim 16 from which claim 20 depends, as discussed above. *See supra* Part IV.D.1. For these reasons, claim 20 would have been obvious in light of Caskey.

Kimpton '93 discloses that "[b]and sizes were generated automatically by comparison with a standard sizing ladder included in every sample." Sun Decl., Ex. 18 (Kimpton '93) at 16. Kimpton '93 therefore reads on the additional limitation of claim 20. Kimpton '93 also reads on independent method claim 16 from which claim 20 depends, as discussed above. *See supra* Part IV.D.1. For these reasons, Claim 20 would have been obvious in view of Kimpton '93.

Claim 4 of the '598 patent depends from claim 1 and recites the same additional limitation as claim 20 of the '660 patent. Sun Decl., Ex. 3 ('598 patent). For the reasons just discussed, claim 4 of the '598 patent would have been obvious in view of Caskey and Kimpton '93.

Claim 12 of the '235 patent depends from claim 1 and recites the identical additional limitation as claim 20 of the '660 patent. Sun Decl., Ex. 4 ('235 patent). Claim 16 of the '235 patent depends from claim 13 and recites the identical additional limitation of claim 12. Id. For the reasons just discussed, claims 12 and 16 of the '235 patent would have been obvious in view of Caskey and Kimpton '93.

5. Claim 21 of the '660 Patent and Claim 5 of the '598 Patent Would Have Been Obvious in View of Caskey and Kimpton '93

Claim 21 of the '660 patent depends from claim 16 and recites the additional limitation "wherein the amplified alleles are evaluated using polyacrylamide gel electrophoresis to separate the alleles, forming a polyacrylamide gel of separated alleles." Sun Decl., Ex. 2 ('660 patent).

Caskey discloses photographic images of polyacrylamide gels and further, explains that "[t]he relative mobilities of the strands are influenced by the composition of the polyacrylamide gel." Sun Decl., Ex. 19 (Caskey), Fig. 3 and col. 13, ll. 42-44. Caskey therefore reads on the additional limitation of claim 21. Caskey also reads on independent method claim 16 from which claim 21 depends, as discussed above. *See supra* Part IV.D.1. For these reasons, claim 21 would have been obvious in view of Caskey.

Kimpton '93 discloses that amplified alleles "were detected by laser scanning during electrophoresis on denaturing polyacrylamide gels." Sun Decl., Ex. 18 (Kimpton '93) at 16. Kimpton '93 therefore reads on the additional limitation of claim 21. Kimpton '93 also reads on independent method claim 16 from which claim 21 depends, as discussed above. *See supra* Part IV.D.1. For these reasons, Claim 21 would have been obvious in view of Kimpton '93.

Claim 5 of the '598 patent depends from claim 1 and, similar to claim 21 of the '660 patent, recites the additional limitation "further comprising the step of separating the alleles by denaturing polyacrylamide gel electrophoresis." Sun Decl., Ex. 3 ('598 patent). For the reasons just discussed, claim 5 of the '598 patent would have been obvious in view of Caskey and Kimpton '93.

6. Claim 23 of the '660 Patent and Claims 7, 22, and 31 of the '598 Patent Would Have Been Obvious in View of Caskey and Kimpton '93

Claim 23 of the '660 patent depends from claim 21, which depends from claim 16, and recites the additional limitation "wherein the separated alleles in the polyacrylamide gel are determined by visualizing the alleles with fluorescence analysis." Sun Decl., Ex. 2 ('660 patent).

Caskey describes in Example 7 a multiplex reaction which fluorescent dyes were utilized to achieve "precise allele quantitation." Sun Decl., Ex. 19 (Caskey), cols. 18-20. The results of the multiplex reaction of Example 7 are shown in Figure 5. Id. Fig. 5. Caskey therefore reads on the additional limitation of claim 23. As discussed previously, Caskey also reads on claim 21 from which claim 23 depends, and claim 16 from which claim 21 depends. *See supra* Part IV.D.1. For these reasons, claim 23 would have been obvious in view of Caskey.

In Kimpton '93, "STR loci with overlapping size ranges were differentiated by use of fluorescent dye labels." Sun Decl., Ex. 18 (Kimpton '93) at 16. Kimpton '93 therefore reads on the additional limitation of claim 23. As discussed previously, Kimpton '93 also reads on claims 21 from which claim 23 depends, and claim 16 from which claim 21 depends. For these reasons, claim 23 would have been obvious in view of Kimpton '93.

Claim 7 of the '598 patent depends from claim 5, which itself depends from claim 1. Similar to claim 23 of the '660 patent, it recites the additional limitation "wherein the separated alleles are detected by fluorescence detection." Sun Decl., Ex. 3 ('598 patent). Claim 22 of the '598 patent depends from claim 12, and also recites the additional limitation "wherein the amplified alleles are separated by denaturing polyacrylamide gel electrophoresis, and detected by fluorescent detection." Id. Claim 31 of the '598 patent depends from claim 28 and recites the identical additional limitation of claim 22. For the reasons just discussed, claims 7, 22, and 31 of the '598 patent would have been obvious in view of Caskey and Kimpton '93.

7. Claim 24 of the '660 Patent, Claim 9 of the '598 Patent, and Claims 11 and 17 of the '235 Patent Would Have Been Obvious in View of Caskey and Kimpton '93

Claim 24 of the '660 patent depends from claim 16 and recites the additional limitation "wherein the at least one DNA sample to be analyzed is isolated from human tissue, wherein the human tissue is selected from the group of human tissue consisting of blood, semen, vaginal cells, hair, saliva, urine, bone, buccal sample, amniotic fluid containing placential cells or fetal cells, and mixtures of any of the tissues listed above." Sun Decl., Ex. 2 ('660 patent).

The invention of Caskey "is applicable to any sample from which amplifiable DNA can be extracted. In medical and forensic uses the samples are selected from the group consisting of blood, semen, vaginal swabs, tissue, hair, saliva, urine and mixtures of body fluids." Sun Decl., Ex. 19 (Caskey), col. 3, ll. 29-33; *see also* id., col. 6, ll. 12-21. Caskey therefore reads on the additional limitation of claim 24. Caskey also reads on independent method claim 16 from which claim 24 depends, as discussed above. *See supra* Part IV.D.1. For these reasons, claim 24 would have been obvious in view of Caskey.

In Kimpton '93, "DNA was prepared from whole blood . . . . Blood samples were obtained from unrelated Caucasians, Afro-Caribbeans, and Asians residing within the United Kingdom." Sun Decl., Ex. 18 (Kimpton '93) at 14. Blood is one of the "tissues" recited in claim 24. Kimpton '93 therefore reads on the additional limitation of claim 24. Kimpton '93 also reads on independent method claim 16 from which claim 24 depends, as discussed above. *See supra* Part IV.D.1. For these reasons, claim 24 would have been obvious in view of Kimpton '93.

Claim 9 of the '598 patent depends from claim 1 and recites the same additional limitation as claim 24 of the '660 patent. Sun Decl., Ex. 3 ('598 patent). For the reasons just discussed, claim 9 of the '598 patent would have been obvious in view of Caskey and Kimpton '93.

Claim 11 of the '235 patent depends from claim 1 and recites the same additional limitation as claim 24 of the '660 patent. Sun Decl., Ex. 4 ('235 patent). Claim 17 of the '235 patent depends from claim 13 and recites the same additional limitation as claim 11. For the reasons just discussed, claims 11 and 17 of the '235 patent would have been obvious in view of Caskey and Kimpton '93.

8. Claim 25 of the '660 Patent, Claims 10, 23, and 33 of the '598 Patent, Claims 18 and 19 of the '235 Patent, and Claim 5 of the '771 Patent Would Have Been Obvious in View of Caskey and Kimpton '93

Claim 25 of the '660 patent is an independent claim reciting a "kit" containing primers for co-amplifying "at least three loci." Sun Decl., Ex. 2 ('660 patent).

Caskey provides: "A further aspect of the present invention is the provision of a kit for DNA profiling assays. The kit is comprised of a container having an [sic] oligonucleotide primer pairs for amplifying a [sic] STR [loci]." Sun Decl., Ex. 19 (Caskey), col. 8, ll. 10-13. Further, in the preferred embodiment "6-10 STR primer pairs" are used. Id., col. 8, ll. 13-16. Caskey therefore reads on claim 25 of the '660 patent. As discussed above, Caskey does not impose any limits on the number of loci or the specific loci which may be used in a multiplex reaction. *See supra* Part IV.D.1. Caskey therefore reads on the sets of loci recited in claim 25. For these reasons, claim 25 would have been obvious in view of Caskey.

Kimpton '93 foretells the "routine use of [STR] loci by forensic laboratories for the identification of individuals." Sun Decl., Ex. 18 (Kimpton '93) at 20; *see also* id. (predicting a "discriminatory system . . . for routine forensic use"). These statements would have suggested to one of ordinary skill in the art to make kits for running multiplex reactions (such as Defendants' AmpFlSTR® kits) in order to satisfy the need or "design incentive[]" for a standard protocol for human identification in the forensic field. KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398, 417, 421 (2007). Therefore, claim 25 would also have been obvious in view of Kimpton '93.

Claim 10 of the '598 patent is an independent claim and, like claim 25 of the '660 patent, recites a "kit" containing primers for co-amplifying "at least three" loci. Sun Decl., Ex. 3 ('598 patent). Similarly, claim 23 of the '598 patent is an independent claim and recites a "kit" containing primers for co-amplifying a set of loci. Id. Claim 33 of the '598 patent is an independent claim and recites a "kit" for containing primers for co-amplifying a set of loci. Id. For the reasons just discussed, claims 10, 23, and 33 of the '598 patent would have been obvious in view of Caskey and Kimpton '93.

Claim 18 of the '235 patent is an independent claim and recites a "kit" containing primers for co-amplifying a set of loci. Sun Decl., Ex. 4 ('235 patent). Claim 19 of the '235 patent depends from claim 18 and recites the additional limitation "wherein all of the oligonucleotide primers fin the kit are in one container." Id. For the reasons just discussed, claims 18 and 19 would have been obvious in view of Caskey and Kimpton '93.

Claim 5 of the '771 patent is an independent claim and recites a "kit" containing primers for co-amplifying a set of loci. Sun Decl., Ex. 5 ('771 patent). For the reasons just discussed, claim 5 would have been obvious in view of Caskey and Kimpton '93.

9. Claim 27 of the '660 Patent and Claim 21 of the '235 Patent Would Have Been Obvious in View of Caskey and Kimpton '93

Claim 27 of the '660 patent depends from claim 25 and recites the additional limitation "further comprising a container having reagents for at least one multiplex amplification reaction." Sun Decl., Ex. 2 ('660 patent).

Caskey provides: "An additional enhancement to the kit is the addition of reagents for mPCR [multiplex PCR]." Sun Decl., Ex. 19 (Caskey), col. 8, ll. 18-19. Caskey therefore reads on the additional limitation of claim 27. Caskey also reads on independent kit claim 25 from

which claim 27 depends, as discussed previously. For these reasons, claim 27 would have been obvious in view of Caskey.

Kimpton '93 describes the various reagents used in a multiplex reaction in the "Material and Methods" section, *e.g.*, PARR buffer, *Taq* polymerase, dNTPs, and primers. Sun Decl., Ex. 18 (Kimpton '93) at 14. Kimpton '93 therefore reads on the additional limitation of claim 27. Kimpton '93 also reads on independent kit claim 25 from which claim 27 depends, as discussed previously. For these reasons, claim 27 of the '660 patent would have been obvious in view of Kimpton '93.

Claim 21 of the '235 patent depends from claim 18 and, like claim 27 of the '660 patent, recites the additional limitation "further comprising reagents for at least one multiplex amplification reaction." Sun Decl., Ex. 4 ('235 patent). For the reasons just discussed, claim 21 would have been obvious in view of Caskey and Kimpton '93.

10. Claim 28 of the '660 Patent Would Have Been Obvious in View of Caskey and Kimpton '93

Claim 28 of the '660 patent depends from claim 25 and recites the additional limitation "further comprising a container having an allelic ladder." Sun Decl., Ex. 2 ('660 patent).

Caskey provides: "A further addition to the kit can be a container having a labelled [sic] standards" which, as Caskey explains, "is composed of labeled alleles of the STR loci of interest," *i.e.*, an allelic ladder. Sun Decl., Ex. 19 (Caskey), col. 7, ll. 15-16; col. 8, ll. 17-18. Caskey therefore reads on the additional limitation of claim 28. Caskey also reads on independent kit claim 25 from which claim 28 depends, as discussed previously. For these reasons, claim 28 would have been obvious in view of Caskey.

As previously discussed with respect to claim 20, Kimpton '93 discloses the use of allelic ladders and therefore reads on the additional limitation of claim 28. Kimpton '93 also reads on

independent kit claim 25 from which claim 27 depends, as discussed previously. For the same reasons as claims 20 and 25, claim 28 of the '660 patent would have been obvious in view of Kimpton '93.

Claim 22 of the '235 patent depends from claim 18 and recites the identical additional limitation as claim 28 of the '660 patent. Sun Decl., Ex. 4 ('235 patent). For the reasons just discussed, claim 22 would have been obvious in view of Caskey and Kimpton '93.

11. Claims 29, 30, and 31 of the '660 Patent, Claims 19, 27, and 32 of the '598 Patent, and Claims 9, 10, and 23 of the '235 Patent Would Have Been Obvious in View of Caskey and Kimpton '93

Claim 29 of the '660 patent depends from claim 28, which itself depends from claim 25, and recites the additional limitation "wherein each rung of the allelic ladder and at least one oligonucleotide primer for each of the loci in the set have a label covalently attached thereto." Sun Decl., Ex. 2 ('660 patent). Claim 30 depends from claim 29 and recites the additional limitation "wherein the label is a fluorescent label." Id. Claim 31 depends from claim 30 and recites the additional limitation "wherein the at least one of the oligonucleotide primers has a different fluorescent label covalently attached thereto than some of the other primer pairs in the container." Id.

In Example 7, Caskey provides: "The fluorescent dyes (Molecular Probes, Eugene, OR) used in the assay were (i) NBD aminoheanoic acid for all internal standard markers, (ii) 5-(and-5)-carboxyfluorescein succinimidyl ester for the HUMTH01 $[AATG]_n$ and HUMHPRTB $[AGAT]_n$ loci, and (iii) Texas Red TM sulfonyl chloride for the HUMFABP $[AAT]_n$ locus. Sun Decl., Ex. 19 (Caskey), col. 19, ll. 59-65. Caskey reads on the additional limitation of claim 29 because both the markers and the primers for each locus are labeled. Id. Caskey further reads on the additional limitation of claim 30 because labels are "fluorescent." Id. Caskey further reads on the additional limitation of claim 31 because different labels were used for the HUMTH01

and HUMHPRTB loci on the one hand, and HUMFABP on the other. Id. Caskey further reads on independent kit claim 25 from which claims 29, 30, and 31 depend, as discussed previously. For these reasons, claims 29, 30, and 31 would have been obvious in view of Caskey.

Kimpton '93 describes "primers [that] were labeled with . . . fluorescent dye markers" and an "internal lane standard . . . labeled with the dye ROX." Sun Decl., Ex. 18 (Kimpton '93) at 14-15; *see also* id. Fig. 1. Kimpton '93 reads on the additional limitation of claim 29 because both the standard and the primers for each locus are labeled. Id. Kimpton '93 further reads on the additional limitation of claim 30 because labels are "fluorescent." Id. Kimpton '93 further reads on the additional limitation of claim 31 because different labels were used primers of different loci. For example, the caption to Figure 1 states that for one multiplex, black, blue, and green dyes were used for primers of the loci HUMvWA, HUMTH01, and HUMF13A1, respectively. Id. at 15. Kimpton '93 further reads on independent kit claim 25 from which claims 29, 30, and 31 depend, as discussed previously. For these reasons, claims 29, 30, and 31 of the '660 patent would have been obvious in view of Kimpton '93.

Claim 19 of the '598 patent depends from claim 12 and, similar to claim 31 of the '660 patent, recites the additional limitation "wherein the multiplex amplification reaction includes oligonucleotide primers for each locus in the set of loci selected in step (b), wherein at least one of the oligonucleotide primers for each locus is fluorescently labeled." Sun Decl., Ex. 3 ('598 patent). Claim 27 of the '598 patent depends from claim 23 and recites the additional limitation "wherein one of each of the pair of oligonucleotide primers in the kit is fluorescently-labeled." Id. Claim 32 of the '598 patent depends from claim 31, which itself depends from claim 28, and recites the identical additional limitation as claim 19. Id. For the reasons just discussed, claims 19, 27, and 32 of the '598 patent would have been obvious in view of Caskey and Kimpton '93.

Claim 9 of the '235 patent depends from claim 7, which itself depends from claim 1. It recites the additional limitation "wherein each of the loci co-amplified in the multiplex reaction in step (b) is co-amplified using a pair of primers which flank the locus, wherein at least one primer of each pair has a fluorescent label covalently attached thereto." Sun Decl., Ex. 4 ('235 patent). Claim 10 of the '235 patent depends from claim 9. It recites the additional limitation "wherein at least three of the labeled primers have different fluorescent labels covalently attached thereto." Id. Claim 23 of the '235 patent depends from claim 22, which itself depends from claim 18, and recites the additional limitation "wherein each rung of the allelic ladder and at least one oligonucleotide primer for each of the loci in the set each have a fluorescent label covalently attached thereto, and at least two of the oligonucleotide primers have a different fluorescent label covalently attached thereto than other primers in the container." Id. For the reasons just discussed, claims 9, 10, and 23 of the '235 patent would have been obvious in view of Caskey and Kimpton '93.

12. Claim 6 of the '598 Patent Would Have Been Obvious in View of Caskey and Kimpton '93

Claim 6 of the '598 patent depends from claim 5, which itself depends from claim 1, and recites the additional limitation "wherein the separated alleles are detected by silver staining." Sun Decl., Ex. 3 ('598 patent).

Caskey explains, "Since some forensic laboratories may not have access to fluorescent detection devices, the STR markers can be detected . . . using alternative labeling and detection strategies [f]or example, radioactive and silver staining detection methods, and ethidium bromide staining methods are all applicable." Sun Decl., Ex. 19 (Caskey), col. 20, ll. 39-46. Caskey therefore reads on the additional limitation of claim 6. Caskey also reads on independent method

claim 1 from which claim 6 depends, as discussed previously. *See supra* Part IV.D.1. For these reasons, claim 6 would have been obvious in view of Caskey.

Kimpton '93 discusses fluorescence-based detection as an alternative to older detection technologies such as autoradiography. Sun Decl., Ex. 18 (Kimpton '93) at 20; *see also* PPF ¶ 42 ("By the early 1990s, fluorescence-based detection of PCR amplification products had also begun to supersede older detection technologies such as radioactivity, gel electrophoresis, and autoradiography, allowing for rapid, safe, and sensitive evaluation of PCR products."). Because silver staining was already known at the time of Kimpton '93, it would have been obvious to one of ordinary skill in the art to use silver staining, especially, as suggested by Caskey, if the person of ordinary skill in the art did not have access to a fluorescent detection device. Sun Decl., Ex. 19 (Caskey), col. 20, ll. 39-46. Therefore, claim 6 of the '598 patent would have been obvious in view of Kimpton '93.

13. Claim 8 of the '598 Patent Would Have Been Obvious in View of Caskey and Kimpton '93

Claim 8 of the '598 patent depends from claim 1 and recites the additional limitation "such that the amplified alleles . . . do not overlap." Sun Decl., Ex. 3 ('598 patent). As discussed above with respect to the independent method claims of the Promega patents, the choice of which specific loci to include in a multiplex set is arbitrary. Therefore, one of ordinary skill in the art could arbitrarily select only those loci which do not produce overlapping alleles to include in a multiplex set. Caskey and Kimpton '93 therefore read on the additional limitation of claim 8. Claim 8 also reads on independent method claim 1 from which claim 8 depends, as discussed previously. *See supra* Part IV.D.1. For these reasons, claim 8 would have been obvious in view of Caskey and Kimpton '93.

14. Claims 15, 21, and 24 of the '598 Patent Would Have Been Obvious in View of Caskey and Kimpton '93

Claim 15 of the '598 patent depends from claim 1 and recites the additional limitation "wherein the set of loci co-amplified further comprises HUMvWFA31." Sun Decl., Ex. 3 ('598 patent). Claim 21 appears to be identical to claim 15. Claim 24 depends from claim 23 and recites the additional limitation "wherein the kit contains oligonucleotide primers designed to co-amplify the set of short tandem repeat loci, further comprising HUMvWFA31." Id. As discussed above with respect to the independent method claims of the Promega patents, the choice of which specific loci to include in a multiplex set is arbitrary. As such, Caskey and Kimpton '93 satisfy the additional limitations of claims 15 and 21, which recite a specific locus. Therefore, claims 15, 21, and 24 would have been obvious in view of Caskey and Kimpton '93.

V. CONCLUSION

In light of the foregoing, Defendants respectfully request as follows:

If the Court construes the claim term "a set of . . . loci" as closed, Defendants respectfully request the Court to grant summary judgment of noninfringement, both direct and indirect, of the asserted claims of the Promega patents in favor of Defendants.

If the Court construes the claim term "a set of . . . loci" as open-ended, Defendants respectfully request the Court to grant summary judgment of invalidity of the Promega patents based on lack of enablement under 35 U.S.C. § 112 in favor of Defendants.

If the Court determines that the Promega patents satisfy the enablement requirement, Defendants respectfully request the Court to grant summary judgment of invalidity of the Promega patents based on obviousness under 35 U.S.C. § 103 in favor of Defendants.

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